Review Article

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Impact of Diet and the Gut Microbiome on Neurodegeneration and Regeneration in Neurological Disorders

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Abstract: Recent advances in the field of neurodegenerative disorders point to a possible association between diet, gut microbiota composition and disease incidence. Hence, the so-called *gut-brain axis*, or more precisely the *gut-microbiome-brain axis*, has gained increasing attention. There are several ways in which gut content can impact the central nervous system, i. e. either I) directly via bacterial components and dietary metabolites that are systematically available, II) by intermediates, such as circulating immune cells or III) via direct neuronal connections, i. e. the vagus nerve.

New technologies for the identification of bacteria, like next generation sequencing, are enabling a higher resolution understanding of microbiota composition. Therefore, it is now possible to elucidate direct interactions between the gut microbiome, the metabolome, and the gut-associated immune system. In addition to these interactions and of equal importance are the interdependencies of gut metabolites with cells of the central nervous system. In this review, we discuss how the gut microbiome can promote neuronal regeneration or degeneration, depending on health status and diet, and how its modulation may be exploited for novel therapeutic applications.

Zusammenfassung: Aktuelle Forschungsergebnisse im Bereich neurodegenerativer Erkrankungen deuten vermehrt darauf hin, dass die Ernährung und damit assoziiert die Zusammensetzung des Darm-Mikrobioms einen entscheidenden Einfluss auf die Entstehung und den Verlauf verschiedenster Krankheiten haben. Die sogenannte Darm-Hirn Achse, oder präziser die Darm-Mikrobiom-Hirn Achse hat dadurch deutlich an Aufmerksamkeit gewonnen. Dabei kann der Darm das zentrale Nervensystem auf unterschiedliche Weisen beeinflussen, I) direkt durch bakterielle Bestandteile und Metaboliten von Bakterien, II) durch Manipulation der im Körper zirkulierenden Immunzellen, oder III) durch direkten Kontakt, z. B. über den N. vagus.

Fortschritte auf dem Gebiet der Molekularbiologie, wie das *Next Generation Sequencing* ermöglichen aufgrund ihres hohen Auflösungsvermögens die genaue Identifikation von Bakterien und die Kompositionen ganzer Mikrobiome. Dadurch ist es möglich, die Interaktionen zwischen dem intestinalen Mikrobiom, dem Metabolom und dem Darm- assoziierten Immunsystem detailliert zu erforschen.

In dieser Arbeit diskutieren wir den Einfluss des Mikrobioms, der Ernährung und den damit verbundenen Gesundheitszustand auf die Neuroregeneration. Der Fokus liegt dabei auf der Möglichkeit, wie dieses Wissen in Zukunft für therapeutische Zwecke genutzt werden kann.

Introduction
The gut and its microbiome

Colonization of the human gut by various bacterial species occurs initially during or shortly after birth. Already the method of birth, i. e. by caesarean section or naturally, is the key factor for the abundance (Toscano et al., 2017) and amount of gut bacteria (Huurre et al., 2008). In addition to the vaginal passage (Dominguez-Bello et al., 2010), another factor known to contribute to the origin of gut microbiota, is breast-feeding (Backhed et al., 2015). Also, the possibility of colonization in utero is currently being examined (Willyard, 2018), which is supported by the presence of bacterial DNA in the placenta (Aagaard et al., 2014).

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In humans, the colon is the organ containing the highest number of microbial species (Sender et al., 2016). The majority of these microbes are members of three bacterial *phyla*, referred to as enterotypes, namely *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* (Tap et al., 2009). Due to the enormous number and diversity of these gut-dwelling bacterial species, the human organism is capable of digesting several food-derived nutrients by taking advantage of bacterially-derived enzymes. *Bacteroides thetaiotamicro,* for example, produces a variety of enzymes that can degrade a range of carbohydrates (Xu et al., 2003). This symbiotic relationship that enables a broad range of nutritive sources has figured largely in human evolution. Perhaps the most prominent example involves mitochondria, bacteria that lost their cellular autonomy and became endosymbiotically-derived organelles (Stilling et al., 2014, Archibald, 2015, Raina et al., 2018).

The primary metabolites and end products of bacterial fermentation include short chain fatty acids (SCFA) (Salminen et al., 1998), micronutrients such as vitamins (Fresia Fernandez, 1987), and secondary bile acids (Ajouz et al., 2014). These microbial products diffuse passively, or are actively transported across gastrointestinal tract endothelia, where they become available for downstream organs via blood circulation (Conlon and Bird, 2014). However, this route is not only used by essentially beneficial metabolites, but also by potentially harmful products of pathogenic bacteria or *pathobionts*. However, during a state of healthy homeostasis, or *eubiosis,* these potentially harmful metabolites are less relevant, since non-pathogenic bacteria outnumber, and thus suppress the growth of pathogenic species (Kamada et al., 2012).

In addition to the influence of host genetics (Bonder et al., 2016), use of antibiotics (Dethlefsen et al., 2008), or immune defense (Wang et al., 2015), the contribution of diet is known to be a key regulator of microbial composition (Ley et al., 2008). Diet begins shaping development of the gut microbiome immediately following birth. For example, components of breast milk (as opposed to formula milk) already affect bacterial gut composition in newborns (Harmsen et al., 2000). During the first three years of life, this composition of bacterial communities evolves towards those found in adults. Furthermore, the composition of fecal microbiota differs between human populations of different origins, highlighting the influence of additional selective pressures, such as dietary habits, hygiene, and general lifestyle, i. e. exercise and smoking. Additionally, gut bacterial diversity increases, in a population-independent manner, during adolescence (Yatsunenko et al., 2012).

The effect of dietary change on the microbiome, as an important environmental factor, depends on the duration of change. Short-term alterations in dietary behavior can influence microbial composition without a large effect on the enterotypes. By contrast, sustained and long-lasting changes to diet are able to affect enterotype states (Wu et al., 2011).

In general, a typical human diet consists of three major components, i. e. carbohydrates, proteins, and fat, which also serve as different substrates for our gut bacteria. In the Western diet these substrates upon reaching the colon, mainly consist of dietary fibers, which comprise non-starch polysaccharides. Additional substrates found here include simple sugars, oligosaccharides, starch, proteins, and lipids (Conlon and Bird, 2014). Importantly, consuming a high amount of dietary fiber is beneficial for health, as it has been shown repeatedly to reduce risk of coronary heart disease (Liu et al., 1999) and diabetes (Montonen et al., 2003). Furthermore, organic acids, the resulting end products of carbohydrate catabolism, serve as additional energy sources for resident bacteria. It is also here where SCFA, in particular, exert a vast number of effects, especially by acting on the immune system once they have been absorbed by the gut epithelium (Conlon and Bird, 2014). However, the direct effects of SCFA on the central nervous system (CNS), need to be better understood.

Dysbiosis and disease

Symbiosis between the commensal microbiome and the innate and adaptive immune system has provided crucial developmental advantages in eukaryote evolution. Hence, it is not surprising, that a dysbalance of the microbiome composition, also denoted as *dysbiosis*, exerts detrimental effects on human health and immunity (Levy et al., 2017). A dysbiosis of the gut microbiome can be caused by internal or external factors, such as sleep deprivation, stress, use of antibiotics, or dietary components (Dethlefsen et al., 2008, Bailey et al., 2011, Devkota et al., 2012) and an increasing number of chronic disorders are associated with an altered microbial composition. For instance, high salt intake exacerbates disease activity in several – mainly autoimmune – diseases, mediated by an increase in pro-inflammatory immune cell subsets (Jorg et al., 2016).

The commensal microbiome essentially participates in regulating the immune tolerance (Weiner et al., 2011). As such, regulatory immune components such as regulatory T cells (Treg) are crucial for development of a sufficient immune tolerance, especially towards enteric microbiota

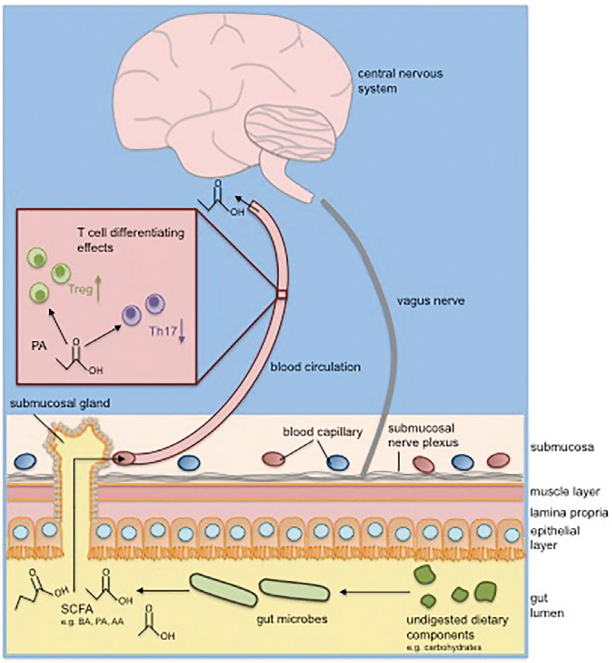

Fig. 1: Microbiome metabolites differentially affect the immune and the central nervous system Short chain fatty acids (SCFA) are metabolites, originating from the fermentation of fiber-rich diet by the commensal gut bacteria. SCFA serve as an energy source for gut epithelia, but also pass from the gut lumen into blood circulation and interact with immune cells within the lamina propria cells of the submucosal nerve plexus. The impact of short chain fatty acids within the CNS is indirect in the case of a shifted immune cell balance towards Treg. Especially in diseases with a disrupted blood-brain-barrier, such as MS, changes in CNS-resident immune cells can directly affect the CNS. BA, butyric acid, PA, propionic acid, AA, acetic acid.

(Sakaguchi et al., 2008). Pathobionts occur at low abundances in healthy individuals, but tend to expand in the diseased organism, as is the case for inflammatory bowel disease (IBD). IBD is characterized by chronic inflammation of the gastrointestinal tract (de Souza and Fiocchi, 2016), leading to a compositional shift in the commensal microbiome (Frank et al., 2007, Lupp et al., 2007, Butto et al., 2015).

Besides gastrointestinal and autoimmune diseases, a dysbiotic state is currently discussed in neurodegenerative disorders. An important microbiome-related metabolic pathway – the kynurenine pathway – for example, was shown to be associated with several neurodegenerative and neuroinflammatory diseases, and depression (Lombardi et al., 2018). For decades, the focus in chronic diseases, such as autoimmune and neurodegenerative diseases has been on the association with a genetic predisposition. However, more recently the direct impact of environmental factors like the microbiome composition has gained attention (Chen et al., 2016b). The microbiome involvement is further supported by animal studies, showing an attenuation or even the complete absence of neurologic disease, once the animals were kept under bacteria-free conditions (Wu et al., 2010, Berer et al., 2011). Human migration studies have demonstrated that multiple sclerosis (MS) incidence increases in subjects who move from low risk countries to countries with higher MS prevalence, usually countries far north of the equator (Gale and Martyn, 1995). This notion initially led to the *theory of latitude*, i. e. reduced sun exposure being the major risk factor, not considering dietary habits. How certain components of the diet may have an impact on neuroinflammation and –degeneration was recently shown for fatty acids, especially the differential roles of short versus long chain fatty acids (SCFA, LCFA). We could show, that administration of LCFA in the experimental model of MS worsened disease course via polarization towards T-helper (Th) 1 and Th17 cells, whereas the SCFA propionic acid diminished clinical symptoms due to an increase of intestine-derived Treg (Haghikia et al., 2015).

Additionally, the observed conversion to a rather anti-inflammatory environment by propionic acid treatment is accompanied with a decrease in demyelination and less axonal loss, which we observed during disease course in mice by Luxol Fast Blue and Bielschowsky silver staining (Haghikia et al., 2015). The question, if these neuroprotective effects are only mediated by reduced inflammation or via a local action of propionic acid on CNS cells, remains unanswered. A recent study has shown that Treg are able to directly increase neuronal remyelination and oligodendrocyte differentiation, thereby affecting remyelination processes (Dombrowski et al., 2017). In addition, anti-inflammatory cytokines like interleukin-10 are capable to trigger neuroregeneration (Chen et al., 2016a). There is cumulative evidence for the neuroprotective capacity of (mainly regulatory) immune-mediated processes, nevertheless, various findings point to a direct neuroprotective effect by commensal metabolic components. However, these components can also exert damaging effects on neurons, especially in high concentrations. In animal models investigating autism-like diseases, administration of high dose propionic acid (e. g. 500 mg/kg body weight), provoked autism-like behavior (Macfabe, 2012, Choi et al., 2018). This corresponds with findings within the disease propionic-acidemia, which is characterized by a reduced activity of the propionyl-CoA carboxylase, leading to an impaired metabolism of propionic acid, accompanied with propionic acid accumulation. This observed autism-like behavior is supposed to be triggered by an increased in-

hibitory GABA-ergic neurotransmission (Morland et al., 2018).

Apart from secondary neurodegeneration as a result of inflammation, in patients with Parkinson's disease, a dysbiosed microbiota has been observed, that is characterized by a reduced abundance of *Prevotellaceae*. Furthermore, changes in Parkinson's patients' microbiome also correlate with disease progression (Minato et al., 2017): the relative abundance of *Enterobacteriaceae* is associated with motor dysfunction (Scheperjans et al., 2015). Additionally, psychiatric diseases such as depression and autism spectrum disorders (ASD) have also been linked to alterations of the gut microbiome (Kang et al., 2013, Jiang et al., 2015). By high-throughput pyrosequencing of bacterial genomic DNA extracted from fecal samples of patients with major depressive disorder, an increase in the levels of *Bacterioidetes*, *Proteobacteria*, and *Actinobacteria* was found, while the level of *Firmicutes* was decreased in comparison to healthy controls. Furthermore, the severity of depressive symptoms is inversely correlated with a reduction of *Faecalibacterium*. ASD have also been linked to a less diverse gut microbiome and to alterations in different bacterial genera, namely reduced abundances of *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae* (Kang et al., 2013), as well as to gastrointestinal disruption that correlates with disease severity (Adams et al., 2011). Therefore, the effect of microbiota transfer therapy has been investigated in a clinical trial. After a 2-week antibiotic treatment followed by bowel cleanse and a subsequent performance of fecal microbiota transplantation, patients displayed a reduction of gastrointestinal symptoms, accompanied by a significant improvement in behavioral ASD symptoms (Kang et al., 2017). Although this example promises hope for fighting other diseases that have been associated with an altered microbiome, it also needs to be assessed carefully. Since most of the microbiome sequencing studies lack a temporal and causal relationship between microbial alterations and disease initiation, the use of probiotics and fecal transplant therapies is still a matter of debate. It is not yet understood, if depleting disease-associated pathogens, by probiotics or fecal transplants, will have any positive effect on these diseases (Khoruts and Sadowsky, 2016).

In contrast to the aforementioned correlations between an altered gut microbiome and neurologic diseases, a healthy diet is associated with lower risk of first clinical diagnosis of central nervous system demyelination; a healthy diet defined as rich in vegetables, legumes, fish, poultry, and eggs (Black et al., 2018).

Interactions between gut and the brain

The term *gut-brain axis* has emerged from observing the direct effects of gut metabolites on the CNS and accordingly, the interaction between the gut and the enteric nervous system is well worked out. Classically, the interaction has long been understood as a "ONE WAY" process concerning the regulation of gastrointestinal functions by the brain. The sympathetic and parasympathetic nervous system modulates gut function, e. g. motility or secretion of several components into the gut lumen (Rhee et al., 2009). However, the impact is reciprocal, and this facet has only recently gained attention (Mayer et al., 2014). Besides the beneficial effects of gut-derived SCFA on the CNS via the immune system, other bacterial products have long been known to directly manipulate neurons. Botulinum and tetanus neurotoxins are bacterial toxins, which directly exert severe damage in neurons. Botulinum toxin blocks synaptic vesicle fusion and the release of neurotransmitters (Rossetto et al., 2014), whereas tetanus toxin is internalized into signaling endosomes and retrogradely transported to the neuronal soma, where it blocks neurotransmission (Calvo et al., 2012, Yang and Chiu, 2017). The effects of the many bacterial metabolites on neurons remain to be explored, yet scarce evidence suggests that some could affect CNS neurons up to the level of the dopaminergic reward system (Diaz Heijtz et al., 2011).

These recent findings on the direct effects of gut metabolites on the CNS have initiated a paradigm shift also in drug development programs targeting (De Vadder et al., 2014, Stilling et al., 2016, Hoyles et al., 2018) Parkinson's, Alzheimer's and MS diseases (Berer et al., 2011, Hill et al., 2014, Sampson et al., 2016). The molecular mechanisms by which SCFA are able to directly influence cellular processes have also been analyzed in cancer research (Augenlicht et al., 2002, Matthews et al., 2012). These mechanisms are mediated either by receptor activation or by epigenetic modulation. SCFA activate the orphan G-protein coupled receptors (GPR) 41 and 43, also known as free fatty acid receptor (FFAR) 2 and 3 (Brown et al., 2003) among other effects, modulating the induction of immune regulatory mechanisms such as Treg differentiation (Smith et al., 2013). Due to their small molecular size, SCFA have also been shown to directly inhibit epigenetic modifiers like the histone deacetylases (HDAC) of class I and II (Candido et al., 1978, Davie, 2003, Harrison and Dexter, 2013). For instance, the key players active in maintaining homeostasis of lysine acetylation are histone acetyltransferases (HATs) and HDACs. HATs catalyze the transfer of an acetyl-group

from acetyl-CoA onto lysine residues of histone proteins. This process leads to a relaxation of nuclear chromatin structure. By contrast, HDACs remove acetyl groups from lysine residues, causing chromatin condensation. Changing the conformation of the chromatin framework either increases (relaxation) or decreases (condensation) transcriptional processes (Chuang et al., 2009). HDAC inhibitors promote chromatin relaxation and thus translational activation. Since acetylation is not exclusively limited to chromatin but also in various proteins as post-translational modifications, HDAC inhibitors may exert varying effects on cellular processes. These effects include modulation of protein expression and function, mitochondrial behavior, intracellular transport, and metabolic processes (Kazantsev and Thompson, 2008). Protein post-translational modifications are discussed as important drivers of neurodegenerative diseases, since they could serve as a link for the gap between environmental factors and genetic disease susceptibility. An imbalance of HAT and HDAC activity is considered to favor neurodegenerative conditions (Chuang et al., 2009). Assuming that SCFA manipulate neurons by HDAC inhibition, our daily diet may have a greater impact on the development of, not just autoimmune diseases, but also neurodegenerative disorders. Beneficial effects of chromatin remodeling have already been shown in an Alzheimer's disease model, using the HDAC inhibitor sodium 4-phenylbutyrate (Ricobaraza et al., 2009). Although there is sparse evidence that SCFA induce direct neuroregenerative effects, an altered HDAC activity has already been proven to participate in processes including neuronal damage. For instance, nuclear export of HDAC1 induces axonal damage that leads to to neuronal death (Kim et al., 2010). Hence SCFA, like known HDAC I and II inhibitors, may prove to have therapeutic potential.

Potentially indirect neuroprotective effects of SCFA include the secretion of anti-inflammatory cytokines such as interleukin-10 from Tregs, and interleukin-4 from Th2 cells. These cytokines have been shown to protect damaged neurons and synapse formation after brain injury (Siffrin et al., 2010, Chen et al., 2016a, Vogelaar et al., 2018).

The presence and composition of our commensal microbiome not only participates in normal gastrointestinal function, but may also influence development of the brain, its function and the occurrence of its diseases. This is important, not only considering maintenance of a healthy diet in order to promote proper brain functioning, but most importantly for expecting mothers, who by maintaining a balanced diet can encourage a child's normal brain development during pregnancy. It was demonstrated in mice that a maternal diet high in fat negatively impacts the offspring's social behavior, caused by a reduction of oxytocin-immunoreactive neurons and a reduction of long term potentiation in dopaminergic neurons within the ventral tegmental area (Buffington et al., 2016). By contrast, a diet containing omega-3 polyunsaturated fatty acids has beneficial impacts on neurodevelopment by influencing the hypothalamic-pituitary-adrenal (HPA) axis. Since the HPA axis mainly determines stress reactivity, these metabolic components prevent depressive-like behaviors due to better stress resistance (Pusceddu et al., 2015). Hence microbiome manipulation, either by diet or by specific prebiotics, may open new therapeutic avenues for treating various systemic diseases including neurodegeneration.

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