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The Role of the Gut Microbiome in Neuroinflammation and Chemotherapy-Induced Peripheral Neuropathy

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most debilitating adverse effects caused by chemotherapy drugs such as paclitaxel, oxaliplatin and vincristine. It is untreatable and often leads to the discontinuation of cancer therapy and a decrease in the quality of life of cancer patients. It is well-established that neuroinflammation and the activation of immune and glial cells are among the major drivers of CIPN. However, these processes are still poorly understood, and while many chemotherapy drugs alone can drive the activation of these cells and consequent neuroinflammation, it remains elusive to what extent the gut microbiome influences these processes. In this review, we focus on the peripheral mechanisms driving CIPN, and we address the bidirectional pathways by which the gut microbiome communicates with the immune and nervous systems. Additionally, we critically evaluate literature addressing how chemotherapy-induced dysbiosis and the consequent imbalance in bacterial products may contribute to the activation of immune and glial cells, both of which drive neuroinflammation and possibly CIPN development, and how we could use this knowledge for the development of effective treatment strategies.

Key Words:

CIPN pathology, chemotherapy-induced dysbiosis, metabolites and neurotransmitters, peripheral mechanisms of CIPN, CIPN treatments

Declaration of Interest Statement: none

1. Introduction:

According to WHO epidemiologic predictions, cancer malignancies will become the leading cause of mortality by 2030, exceeding ischemic heart disease deaths by more than 2-fold (Mattiuzzi & Lippi, 2019). Nearly all cancer patients receive chemotherapeutic intervention as a treatment option that consists of a combination of different chemotherapy agents (Goffin et al., 2010; Kaufmann et al., 2006; Louvet et al., 2002; Okines et al., 2010; Wagner et al., 2006). Since the first use of chemotherapeutics as cancer treatments in the 1940s, the survival prognosis of cancer patients has improved drastically, and these agents have proven to be very effective in reducing cancer-related morbidity and mortality. However, chemotherapy agents are very toxic, with little selectivity for cancer cells, and therefore, cause substance-specific and dose-dependent side effects (Tay et al., 2022). A major hurdle impacting the utility of these agents is untreatable peripheral neuropathy, which often leads to dose reductions or discontinuation of chemotherapy treatment which, in turn, impede the clinical application of otherwise beneficial therapy (Areti et al., 2014; Escalante et al., 2017). For example, chemotherapy-induced peripheral neuropathy (CIPN) develops in over 90% of cancer patients treated with vincristine, cisplatin, or oxaliplatin (Argyriou et al., 2013; Cersosimo, 2005; Krarup-Hansen et al., 2007; Ramchandren et al., 2009; Roelofs et al., 1984; Seretny et al., 2014; Toopchizadeh et al., 2009) and manifests as sensory-motor symptoms, including neuropathic pain, and long-term motor impairment (Seretny et al., 2014; Starobova & Vetter, 2017). The incidence of CIPN varies across the range of chemotherapy drugs. Additionally, the reported incidences for a specific drug, for example vincristine, may vary between 60-90% (Ramchandren et al., 2009; Seretny et al., 2014; Toopchizadeh et al., 2009). This variability in the reported incidence of chemotherapy drugs can be attributed to study design and the inability to control for factors such as age, genetic factors, lifestyle, sex, cancer type, patient comorbidities, and past chemotherapy treatments, all of which may contribute to the development of CIPN (Kandula et al., 2016; Molassiotis et al., 2019; Seretny et al., 2014). Furthermore, chemotherapy drugs are always administered as combination regimens, with often unknown contribution of the single drug to CIPN.

Although researchers have been trying to delineate CIPN pathology for decades, the underlying mechanisms causing CIPN, which include neuroinflammatory processes, are still poorly understood, hampering the development of effective treatment strategies (Starobova & Vetter, 2017). The contribution of the gut microbiome to neuroinflammatory processes, including those driving CIPN development, is an emerging research area that may provide novel yet unexplored treatment options for CIPN management. Gut microbiota are bacteria and archaea that reside in the digestive tract. The gut microbiota exercise several functions, such as inhibition of pathogens and maintaining the intestinal epithelium, but also contribute to regulating the function and development of the immune and nervous system (Gomez de Aguero et al., 2016; Mazmanian et al., 2005; Tan et al., 2016). Recent studies suggest that microbiota can regulate the release of cytokines, chemokines, neurotransmitters, and neuropeptides, modulate neural messages carried by the vagal and spinal afferent neurons, and regulate mood, behaviour, and therapeutic efficacy of chemotherapy drugs (Bengmark, 2013; Cheng et al., 2020; Farmer et al., 2014). All these processes rely on a specific balance in the composition of gut microbiota. Chemotherapy agents create dysbiosis, and even subtle changes in the sensitive "gut ecosystem" can directly influence the function of the immune and endocrine systems and modulate the function of the central and peripheral nervous systems (CNS and PNS) (Viaud, Flament C Fau - Zoubir, et al.; Viaud, Saccheri F Fau - Mignot, et al.; Zhong et al., 2019). Importantly, oxaliplatin- and paclitaxel-induced neuropathy is alleviated in mice pretreated with antibiotics eradicating the microbiome, suggesting that the gut microbiome may contribute directly to CIPN pathology (Ramakrishna et al., 2019; Shen et al., 2017).

In this review, we describe the communication pathways between the microbiome and the nervous system, and address chemotherapy-induced dysbiosis. Finally, we critically discuss the current understanding of the gut microbiome's contributions to inflammation and CIPN pathology with the main focus on peripheral mechanisms. Additionally, we discuss future avenues for CIPN treatment using microbiome-modulating strategies.

2. Bi-directional communication between gut microbiome and nervous system

The communication pathways between the gut microbiome and the nervous system are bidirectional and involve the brain, hypothalamic pituitary adrenal axis, spinal cord, and autonomic and enteric nervous (together gut-brain axis) and immune systems (Morais et al., 2021). Gut microbiome products, such as pathogen-associated molecular patterns (PAMPS), metabolites and neurotransmitter precursors, can be directly detected by enteric neurons, inducing transmission of the signals to the rest of the enteric nervous system (ENS), PNS, and CNS via enteric, spinal and vagal pathways (**Figure 1A**) (Mao et al., 2013; Muller et al., 2020; Strandwitz et al., 2019; Sudo et al., 2004; Yano et al., 2015). Neurones within the human ENS interact with various cells, including muscle, epithelial, and immune cells (**Figure 1B**) (Fleming et al., 2020; Gulbransen & Sharkey, 2012). The ENS contains around 100 million neurons, which differ in type and distribution depending on the region and species and include sensory, motor, and interneurons that form synaptic connections for the flow of information from sensory neurons to interneuronal networks to motor neurons and, finally, effector neurons (Hansen, 2003) (**Figure 1B**).

The ENS densely populates the mucosa thereby allowing for interaction either directly or indirectly with the gut microbiome (Chesne et al., 2019). Intrinsic primary afferent neurons (IPANs) detect chemical and mechanical stimuli originating in the gut lumen and transmit them to surrounding enteric nerves (Veiga-Fernandes & Mucida, 2016). Axons of IPANs extend into the gut mucosa allowing for the detection of bacterial products such as lipopolysaccharides (LPS) (Collins, 1996; Mao et al., 2013). The ENS also has two major ganglionated plexuses: the myenteric plexus between the longitudinal and circular muscle and the submucous plexus between the circular muscle and mucosa (**Figure 1B**). Most motor neurones innervating the circular and longitudinal muscle are found in the myenteric plexus and play a significant role in gastrointestinal (GI) motility (Costa et al., 2021). The submucous plexus also communicates with the myenteric plexus through axons forming a functionally integrated unit (Costa et al., 2000). Both plexuses contain neural cell bodies connected to interganglionic nerves that project to the muscle layers (Furness, 2012). The myenteric ganglia are found throughout the GI tract, while the submucosal ganglia are sparse/absent in the stomach and oesophagus but present in the rest of the GI tract (Brehmer et al., 2010). Similar to astrocytes in the CNS and Schwann cells in the PNS, enteric glia cells, specifically submucosal ganglia, have important roles in maintaining the function and the

survival of enteric neurons and modulating the immune system (Abdo et al., 2010; Ibiza et al., 2016). In addition, enteric glia play important roles in motility, inflammation, intestinal epithelial barrier integrity and enteric neurotransmission, maintaining and regulating GI homeostasis (Boesmans et al., 2015; Grubisic & Gulbransen, 2017; Van Landeghem et al., 2009). Due to its close proximity, the microbiome modulates the initial colonisation, homeostasis, function and activation of enteric glia in the lamina propria (Brun et al., 2015; Kabouridis et al., 2015; Turco et al., 2014). Enteric glia also have an important role in the maintenance and regulation of the intestinal epithelial barrier integrity and inflammation through the secretion of mediators, such as the glial-derived neurotrophic factor (GDNF) modulating differentiation, proliferation and adhesion of intestinal epithelial cells (Neunlist et al., 2007; Van Landeghem et al., 2009). The dysregulation of enteric glia function by chemotherapy may contribute to gut leakage and the entry of microbiome metabolites into the systemic blood. Enteric glia express major histocompatibility complex (MHC) class I and class II molecules and, as antigen-presenting cells, interact with other immune cells and modulate the immune response in the gut and the system by secreting various inflammatory cytokines and mediators such as interleukins (IL), nitric oxide (NO) and GDNF (Bassotti et al., 2012; da Silveira et al., 2011; Geboes et al., 1992; Koretz et al., 1987; Ruhl et al., 2001; Xiao et al., 2014). The ENS also contains immune cells, including resident macrophages, neutrophils, dendritic cells and T-cells, that regulate the homeostasis and survival of enteric neurons, release of growth factors and inflammatory processes, partially regulating ENS function (Asano et al., 2015; Hadis et al., 2011; Kuhl et al., 2007; Kulkarni et al., 2017).

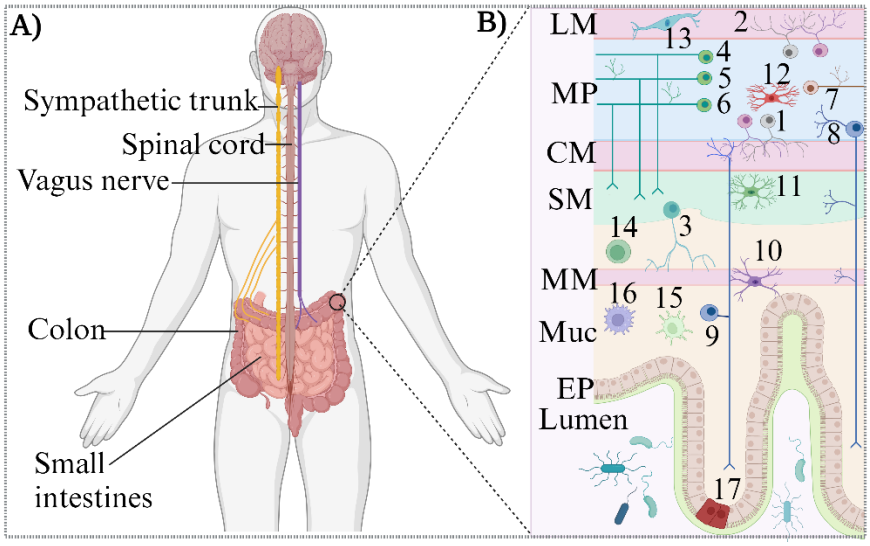


***Figure 1**: Simplified anatomy of the gut-brain axis and the enteric nervous systems. **(A)** Gut-brain axis: the enteric nervous system receives input from the vagus nerve allowing for direct gut-brain communication. **(B)** Neuronal components of the enteric circuitry and the surrounding cells include networks of interconnected intrinsic sensory neurons (IPANs) that detect mechanical distortion and luminal chemistry, and form interconnected networks encompassing the circumference of the gut wall, providing innervation of the mucosa (Muc). These synapse with descending and ascending interneurons. Within the myenteric plexus (MP), interneurons form chains along the length of the gut, with ascending interneurons projecting orally and descending interneurons projecting in aboral direction. Myenteric excitatory muscle motor neurons and inhibitory muscle motor neurons innervate circular (CM) and longitudinal muscle (LM). Enteric glia and immune cells, including macrophages, dendritic and T-cells regulate the microenvironment surrounding enteric neurones. SM: submucosal plexus, EP: Gut epithelium. Neuron Types: (1) inhibitory and excitatory longitudinal muscle motor neurons; (2) Inhibitory and excitatory circular muscle motor neurons; (3) motor neuron to the muscularis mucosa; (4) descending interneurons (local reflex); (5) descending interneurons (secretomotor and motility reflex); (6) descending interneurons (migrating myoelectric complex); (7) ascending interneurons; (8) myenteric intrinsic primary afferent neurons (IPANs); (9) submucosal IPANs; other cell types: (10) mucosal enteric glia (Type III); (11) interganglionic enteric glia (Type I); (12) interganglionic enteric glia (Type II) ; (13) intra-muscular enteric glia (Type IV), (14) T cell; (15) dendritic cell; (16) macrophage; (17) enteroendocrine cells. Adapted from (Fleming et al., 2020) and (Gulbransen & Sharkey, 2012).*

During pathological states that increase intestinal wall permeability such as chemotherapy-induced mucositis or ulcers, LPS or bacterial RNA can penetrate into the mucosa activating resident antigen-presenting cells (APCs) - macrophages and dendritic cells - via pattern recognition receptors driving inflammatory processes (Balmer et al., 2014; Khosravi et al., 2014). These cells can then activate lymphocytes, such as T-cell, which then reach the systemic circulation and the lymph nodes, orchestrating further inflammatory processes and systemic cytokine release. Bacterially derived products can be transported by colonocytes using specific transporters – such as the sodium-dependent

monocarboxylate transporters transporting monocarboxylic acids produced by bacteria – into the systemic circulation to reach other organs, including the PNS and the immune system (Caetano-Silva et al., 2023; Le Poul et al., 2003; Usami et al., 2008). Specifically, the microbiome-derived bacteria produce neurotransmitters such as γ-aminobutyric acid (GABA) or glutamate (Wu & Shah, 2017; Yang & Yang, 2017) and releases metabolites such as short-chain fatty acids that activate enteroendocrine cells to release gut hormones, such as glucagon-like peptide-1 (GLP-1) (Lebrun et al., 2017; Tolhurst et al., 2012). Additionally, microbiome-derived bacteria activate immune cells to release cytokines including interleukin-1 (IL-1) and tumour necrosis factor (TNF) (Enamorado et al., 2023; Petra et al., 2015). These molecules then enter the systemic circulation, consequently modulating the function of the ENS and CNS but also impacting the function of peripheral sensory nervous systems (Chen et al., 2022). Peripheral sensory neurons play an important role in mediating CIPN symptoms, including mechanical and thermal hyperalgesia, numbness, and tingling. The cell bodies of the pseudounipolar sensory neurons are located in the dorsal root ganglia (DRG) and project axons into the spinal cord, and nerve terminals into the periphery, including the skin. The nerve terminals of sensory neurons can be activated by external stimuli such as cold, pressure, vibration, or touch, as well as internal chemical signals such as inflammatory mediators, hormones, or neurotransmitters. This is achieved through the expression of a vast range of specialised receptors and ion channels, such as the serotonin receptors (5HT), prostaglandin E receptors (PGE 1-4), toll-like receptors (TLRs), interleukin-1 receptor (IL-1R), tumour necrosis factor receptor (TNFR), glycoprotein 130 (gp130, receptor for IL-6) and transient receptor potential (TRP) and voltage-gated ion channels (reviewed in (Jami et al., 2017)and (Pinho-Ribeiro et al., 2017)). These receptors and channels also facilitate communication with other cells, including satellite glia cells, Schwann cells, macrophages, fibroblasts, and keratinocytes, which exist in and closely regulate the neuronal microenvironment (reviewed in (Starobova et al., 2022)). Upon detection of stimuli, the signal is transmitted from the nerve ending to the dorsal root ganglia, the spinal cord, and finally to the somatosensory cortex in the CNS.

The relationship between the microbiome and CNS function is undisputed, and evidence demonstrates that microbiome composition affects CNS function and development and, hence, central pain

processing (Erny et al., 2015; Mulder et al., 2023; Needham et al., 2020). The so-called gut-brain axis, which includes the brain, hypothalamic pituitary adrenal axis, spinal cord, and autonomic and enteric nervous system, involves various chemical and hormonal pathways and is the main connection allowing for the bidirectional flow of information between the CNS and the microbiome (reviewed in (Morais et al., 2021)). We acknowledge that chemotherapy-induced dysbiosis impacts CNS function, contributing to altered pain processing and CIPN development; however, as our review focuses on peripheral mechanisms driving CIPN, there is limited scope for additional in-depth discussion regarding this topic. Therefore, we refer the reader to additional excellent reviews covering this area (Pane et al., 2022), (Park & Kim, 2021),(Cryan et al., 2020), (Guo et al., 2019) and (Cryan & Dinan, 2012).

In addition to effects of the gut microbiome and its products on the CNS and PNS, the GI tract and consequently the microbiome are also affected by the CNS and PNS. Specifically, enteric function is controlled by the CNS via efferent pathways including the vagus nerve, which provides excitatory function, and the sympathetic trunk, which provides inhibitory function (Carabotti et al., 2015; Furness et al., 2014; Schemann & Grundy, 1992). Moreover, stressful signals, such as pain, can activate the hypothalamic pituitary adrenal axis (HPA), leading to the release of the corticotropin-releasing factor (CRF) from the hypothalamus, which stimulates adrenocorticotropic hormone (ACTH) secretion from the pituitary gland that, in turn, mediates cortisol release from the adrenal glands (Van de Kar & Blair, 1999). Chronic stress due to high cortisol levels then impacts the function of other organs, including the GI tract, and changes microbiota composition and diversity (Bailey & Coe, 1999). Specifically, chronic stress impacts the release of gastric hormones, such as gastrin, somatostatin and motilin, dysregulating postprandial GI motility, mucus and biofilm production in the GI tract, consequently modulating the diversity and activity of the microbiome (Clarke et al., 2006; Galley et al., 2014; Gue et al., 1989; Guthrie & Nicholson-Guthrie, 1989; Hughes & Sperandio, 2008; Rubio & Huang, 1992).

3. The contribution of the microbiome to neuroinflammation and CIPN

3.1. Neuroinflammatory mechanisms contributing to CIPN.

The role of immune cells, such as leukocytes, and neuroglia, such as satellite glial cells, microglia, and astrocytes, in CIPN following some of the chemotherapy drugs, such as vincristine and paclitaxel, is

well established (see (Tay et al., 2022) and (Starobova et al., 2022) for detailed reviews). Monocytes/macrophages circulate through or reside (respectively) in all nerves, including the nerves that form the gut-brain axis and peripheral sensory nerves, regulate the neuronal microenvironment, and play an important role in CIPN development. Specifically, vincristine and paclitaxel-induced peripheral neuropathy involve an increase of $F4/80^+$-expressing (pan monocyte/macrophages marker) cells in peripheral nerves and the subsequent release of cytokines such as interleukin-1 beta (IL-1β), interleukin 6 (IL-6) and tumour necrosis factor (TNF) from these cells. Consequently, the depletion of phagocyting cells, which includes $F4/80^+$ cells, results in the alleviation of CIPN symptoms (Old et al., 2014; Peters et al., 2007; Starobova et al., 2021; Zhang et al., 2016). Similarly, microglia, specialised macrophages residing in the CNS, regulate neuronal development, homeostasis, and recovery from injury by releasing cytokines, chemokines, and neuroactive molecules in response to activation (Davalos et al., 2005; Nimmerjahn et al., 2005; Paolicelli et al., 2011; Tremblay et al., 2010). The activation of microglia and the subsequent release of cytokines and chemokines, including IL-1β, are associated with the development of CIPN following, for example, platinum derivates and taxane (Burgos et al., 2012; Cataldo et al., 2019; Gu et al., 2020; Hu et al., 2018). Microglia also closely communicate with astrocytes within the CNS, further regulating the neuronal microenvironment and contributing to CIPN (see (Starobova et al., 2022) for a detailed review). Wahlman et al. demonstrated that CIPN following oxaliplatin is mediated via Nod-like receptor 3 (NLRP3) activation and IL-1β release from astrocytes (Wahlman et al., 2018). Additionally, paclitaxel-induced neuropathy is associated with increased RNA expression of tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), chemokines such as CCL2, CCL3, , IL-12, CCL11, CCL4, CCL3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in rodent DRGs and spinal cord and breast cancer patients suffering from CIPN have increased levels of IL-6 (Makker et al., 2017; Starkweather, 2010; Zhang et al., 2016). Therefore, neuroinflammation and the release of inflammatory signalling molecules by these cells are well established as a driver of CIPN. It is generally accepted that cytokines released by these activated cells in the proximity of neurons then regulate neuronal signalling and pain perception. For example, IL-1β modulates the function of voltage-gated sodium channels expressed by sensory neurons via p38-mitogen-activated protein kinase (p38-MAPK) pathway, consequently

236 modulating neuronal excitability (Binshtok et al., 2008) and local or systemic injection of IL-1β directly
237 elicits severe hyperalgesia in rodents (Amaya et al., 2006; Ferreira et al., 1988). Moreover, IL-1β and
238 TNF-α induce the expression of cyclooxygenase-2 (COX-2) RNA in dorsal root ganglia neurons while
239 TRPA1 expression appears to be partially modulated by IL-6 (Fehrenbacher et al., 2005; Malsch et al.,
240 2014).

241 Although these studies have demonstrated that neuroinflammation mediated by peripheral immune cells
242 and neuroglia is a major driver of CIPN for some of the chemotherapy drugs, it is not yet understood
243 whether chemotherapy alone is sufficient for the activation of these cells and initiation of these
244 processes. Currently, there is only sparse evidence demonstrating the direct contribution of the
245 microbiome to CIPN. However, considering the important role of the GI microbiota in modulation and
246 maturation of the immune systems, both microbiota-mediated immune priming as well as
247 chemotherapy-induced dysbiosis (pathological microbiome composition), and the consequent changes
248 in immune system activity, may contribute to the above-described neuroinflammatory processes
249 (**Figure 2**) (Gomez de Aguero et al., 2016; Mazmanian et al., 2005; Tan et al., 2016).

250 *3.2. Chemotherapy-induced dysbiosis, Neuroinflammation and CIPN*

251 The intestinal microflora is highly diverse and includes species from dominant commensal phyla such
252 as *Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria* and *Verrucomicroba* (Rinninella et al.,
253 2019) and specific balance between these phyla is important for neuronal development and function.
254 For example, a shift in bacteria species ratio leads to cognitive impairment and behavioural changes in
255 rodents (Cani, 2014; Farmer et al., 2014; Johnson, 2020). Chemotherapy treatments such as cytarabine,
256 doxorubicin, paclitaxel and oxaliplatin cause dysbiosis, resulting in an imbalance in microbiota
257 composition in rodents (**Table 1**). Additionally, etoposide, melphalan, cytarabine, and carmustine
258 reduce the total number of bacteria in patient faeces, decrease the ratio of commensal bacteria, such as
259 *Lactobacillus* and *Bifidobacteria* and increase the ratio of potentially harmful bacteria, such as
260 *Bacteroides* or *Escherichia* (Montassier et al., 2014). These changes in the microbiome composition
261 can modulate inflammatory responses. For example, in rodents, cyclophosphamide decreased the ratio
262 of *Firmicutes* species in the small intestine and induced the translocation of selected species of Gram-

positive bacteria into mesenteric lymph nodes and spleen, stimulating the generation of T-helper (Th) 17 cells and activating Th1 immune response (Viaud, Flament C Fau - Zoubir, et al.; Viaud, Saccheri F Fau - Mignot, et al.). Importantly, treatment with the antibiotic vancomycin lowered polarisation of naïve CD4+ T cells into Th1 and Th17 cells (Viaud et al., 2013). However, most of these studies were performed in rodents, and although the human and rodent microbiota have some similarities, such as domination of *Bacteroides* and *Firmicutes*, the results of these studies should be interpreted with caution (Ley et al., 2005). Nonetheless, dysbiosis can also activate the HPA-axis, via the vagus nerve, further impacting the function of the PNS and CNS (Forsythe et al., 2016; Foster & McVey Neufeld, 2013).

Table 1: Effect of chemotherapy on intestinal microbiota composition.

Chemotherapy drug	**Species**	**Effects on microbiome**	**Ref.**
etoposide, melphalan, cytarabine, carmustine	human	-Decrease of *Lactobacillus* and *Bifidobacteria* -Increase of *Bacteroides* and *Escherichia*	(Montassier et al., 2014)
cyclophosphamide	mouse	-Decrease of *Firmicutes* (*Lactobacillus* and *Enterococcus*)	(Viaud, Flament C Fau - Zoubir, et al.; Viaud, Saccheri F Fau -

			Mignot, et al.)
doxorubicin	mouse	-Decrease of *Bacteroidetes* and *Firmicutes* -Increase of Actinobacteria *Verrucomicroba*, *Bacteroidetes*, and *Firmicutes*	(Bawaneh et al., 2022)
paclitaxel	mouse	-Decrease of *Bacteroidetes* and *Verrucomicrobia*	(Ramakrishna et al., 2019)
oxaliplatin	mouse	Increase of *Verrucomicrobia*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and *Tenericutes*	(Shen et al., 2017)
irinotecan	rat	-Increase of *Proteobacteria*, *Pseudomonadota* and *Firmicutes* -Decrease of *Actinobacteria*, *Bacteroidetes* and *Firmicutes*	(Stringer et al., 2009) (Stringer et al., 2008) (Stringer et al., 2007)

Chemotherapy-induced dysbiosis and consequent bacterial death can also lead to release of PAMPs that activate immune cells to release pro-inflammatory cytokines. For example, culturing human and rodent leukocytes and lymphocytes with bacterial lysates enriched in PAMPs induces the release of inflammatory signalling molecules, including IL-1β, IL-12, IL-10, INF-γ, and IL-17 (de Roock et al., 2011; de Roock et al., 2010; Deng et al., 2016). Chemotherapy drugs may eradicate both pathogenic and beneficial gut bacteria, resulting in the release of PAMPs, such as LPS and flagellin, which are known TLR activators. TLRs belong to intracellular (TLR3, TLR7, TLR9, and TLR8) and extracellular (TLR4, TLR 2, and TLR5) pathogen recognition receptors (PRRs) recognising PAMPs released by bacterial, viral, and fungal pathogens. TLRs are naturally expressed by immune cells, satellite glia, microglia, astrocytes, and neurons (Bsibsi et al., 2002; Diogenes et al., 2011; Marinelli et al., 2015; Mitterreiter et al., 2017; Ritchie et al., 2018; Xu et al., 2015). LPS released by intestinal microbiota enters the systemic circulation through a damaged gut barrier and induces myeloid differentiation primary response 88 (MyD88) or TIR domain-containing adaptor inducing interferon-β (TRIF)-mediated pro-inflammatory signalling and the release of proinflammatory cytokines from immune cells or activates sensory neurons (Boonen et al., 2018; Tulkens et al., 2020). Specifically, in neurons, LPS activates the TLR4/Myeloid differentiation protein-2 (MD2) complex, inducing neurogenic inflammation via calcitonin gene-related peptide (CGRP) release and directly activates sensory neurons via TRP channels such as TRPV1 and TRPA1 (Boonen et al., 2018; Meseguer et al., 2014). Inhibition of TLR4 using the lipopolysaccharide from the photosynthetic bacterium *Rhodobacter sphaeroides* (LPS-RS), a TLR4 and TLR2 inhibitor, attenuates peripheral neuropathy in rats treated with paclitaxel (Li et al., 2015). Additionally, chemotherapy drugs such as doxorubicin and 5-fluorouracil (5-FU) also induce increased expression of TLR receptors in human monocytes via p53-mediated DNA damage (Menendez et al., 2011) and paclitaxel, induces the expression of TLR4 in human and rat dorsal root ganglia which further contributes to increased TLR signalling (Li et al., 2015; Li et al., 2014).

Only few studies have shown a direct link between gut bacteria, immune or glial cell activation and CIPN. For example, Shen et al. demonstrated that gut microbiota and $CD45^{+}$ leukocytes, including

macrophages, promote oxaliplatin-induced mechanical hyperalgesia via TLR4 activation (Shen et al., 2017). Ramakrishna et al. investigated the differences in the severity of paclitaxel-induced neuropathy in C57BL/6 neuropathy-sensitive and 129SvEv neuropathy-resistant mouse strains and linked these to the microbiome diversity of these mouse strains and increased microglia proliferation (Ramakrishna et al., 2019). Additionally, Shi et al. demonstrated that paclitaxel-treated rats had a decreased abundance of *Turicibacter*, *Clostridium,* and *Corynebacterium* that was associated with increased expression of TLR4 and p38-MAPK in spinal astrocytes and CIPN development (Shi et al., 2023).

Microbiome composition also modulates inflammatory signalling and the levels of systemically released cytokines. For example, Schirmer et al. linked inter-individual variation in the cytokine release from human peripheral blood mononuclear cells isolated from healthy individuals to specific microbial organism combinations (Schirmer et al., 2016). Additionally, increased interferon-gamma (IFN-γ) response was observed in the presence of *B.fragilis* and *S.aureus* while *Alistipes spp*.,*Clostridium spp.*, and *Bilophila spp.* reduced LPS-induced TNFα release from human peripheral blood mononuclear cells. On the other hand, treatment of T-cells with *Lactobacillus spp*. induced the release of the anti-inflammatory cytokine IL-10, suggesting that the microbiome also regulates anti-inflammatory responses (de Roock et al., 2010).

3.3. Bacterial Metabolites, Neuroinflammation and CIPN

Intestinal bacteria produce a variety of metabolites, including short-chain fatty acids (SCFAs), such as butyrate (Miller & Wolin, 1996), branched-chain amino acids (BCAAs), such as valerate or isobutyrate (Yamamoto et al., 2022), intestinal enzymes, such as β-glucuronidase (Wallace et al., 2015), vitamins, such as vitamin B complex (Albert et al., 1980), toxins such as *C. perfringens* enterotoxin (Miyamoto et al., 2011; Naylor et al., 1998), and neurotransmitters or neurotransmitter precursors, such as gamma amino butyric acid (GABA) (Duranti et al., 2020; Otaru et al., 2021), and precursors of dopamine (Luqman et al., 2018) and norepinephrine (Tsavkelova et al., 2000). These bacterial products can be either beneficial or harmful to the host and play an important role in nervous system function but also pathological neuroinflammatory diseases such as multiple sclerosis (Berer et al., 2017). Whether

bacterial products are beneficial or harmful is determined by the microbiome composition which consequently determines the amount and type of released metabolites.

Recent evidence also suggests that circulating metabolites and neurotransmitters released by the gut bacteria may contribute to priming and activation of immune and glial cells, which may also possibly contribute to CIPN development. These bacterial products can be used as metabolites or energy sources for the bacteria itself and by cells of the colon and the ileus, or are transported through specific transporters into the systemic circulation to reach other organs, including peripheral and central nerves, glia, and immune cells (for detailed review see (Agus et al., 2021)). For example, SCFAs are absorbed by colonocytes via sodium-dependent monocarboxylate transporters (Caetano-Silva et al., 2023). In colonocytes, SCFAs function as an energy source or are transported into the circulating blood, reaching their targets, such as G protein-coupled receptors (GPCR) or nuclear class I histone deacetylases (HDACs) on various cell types, including immune cells, modulating systemic inflammation (Le Poul et al., 2003; Usami et al., 2008).

Chemotherapy drugs often damage the mucosa, driving the development of mucositis (inflammation of the mucosa, characterised by crypt and villus loss) (Ohsawa et al., 2020), colitis (inflammation in the colon), ulceration of the epithelium, and intestinal perforation. This increases intestinal permeability, allowing bacterial metabolites and products to enter the systemic circulation (Deleemans et al., 2019). For example, irinotecan, used for the treatment of metastatic colorectal cancer, is frequently associated with direct mucosal damage due to its metabolite SN-38-induced cytotoxicity (Swami et al., 2013; Takasuna et al.). After the conversion of irinotecan (CPT-11) to SN-38 in the liver, SN–38 undergoes glucuronate conjugation, changing into inactive SN-38 glucuronide. Later, it is excreted into bile and deconjugated by β-glucuronidases produced by intestinal bacteria to become SN-38 once again (Guthrie et al.). SN-38 causes mucosal damage via prostaglandin and cyclooxygenase (COX)-2-mediated inflammation (Logan et al.). Irinotecan also alters the integrity of the epithelial barrier, as evidenced by decreased mRNA expression of tight junction proteins occludin-1, claudin-1, and zona occludin-1, disrupting paracellular solute and water flux and cell polarity (Fakiha, 2015). Another example is 5-FU, used to treat several cancers, including colorectal tumours. 5-FU is associated with intestinal mucositis

(Longley et al., 2003) and a reduction of the crypt and villus length by inducing enterocyte apoptosis (Avallone et al.; Soares et al.). Possibly, an increased expression of IL-1β drives inflammation and apoptosis of these intestinal cells (Chang et al.; Wu et al.). Additionally, NADPH oxidase (NOX)-dependent reactive oxygen species (ROS) generation in phagocytes following 5-FU treatment leads to intestinal crypt loss (Yasuda et al.). Consequently, chemotherapy induces the death of mucosal cells, leading to the release of danger-associated molecular patterns (DAMPs). DAMPs can activate inflammatory signalling pathways such as the nuclear factor kappa B (NF-kB) (Sonis et al., 2004) and inflammasomes, such as absent in melanoma 2 (AIM2) and Nod-like Receptors (NLRPs) (Lian et al., 2017) in epithelial cells of the GI tract, leading to infiltration of neutrophils, eosinophils, and macrophages in lamina propria (Lian et al., 2017) and further release of pro-inflammatory mediators including chemokines such as CCL2, CXCL1 and cytokines such as IL-1β, IL-18, and IL-6 (Lian et al., 2017). Moreover, chemotherapy-induced systemic release of cytokines and PAMPS released by bacteria can lead to blood-brain barrier (BBB) leakage, possibly allowing the entry of some of these products into the CNS (Konsman et al., 2022; Wardill et al., 2021). For example, LPS-induced peripheral inflammation increased the permeability of BBB and led to an increase of IL-6 and TNF-α in the CNS. However, it is not clear whether the increase of these cytokines in the CNS can be accounted to BBB leakage or to infiltration of immune cells to the CNS (Takeda et al., 2013) .

Chemotherapy-induced dysbiosis can also lead to under-production of bacterial metabolites and neurotransmitter precursors. The most-investigated metabolite in context with neuropathy is the SCFA, butyrate, which inhibits histone deacetylation in immune cells, leading to lower activation of NF-κb and lower production of cytokines (Usami et al., 2008). However, a direct link between chemotherapy-induced dysbiosis, changed butyrate production, and CIPN was not established. Nonetheless, Non-Hodgkin's lymphoma patients treated with alkylating agents, topoisomerase II inhibitors, and anthracyclines had a reduced proportion of butyrate-producing intestinal bacteria of the *Firmicutes* and *Actinobacteria* phyla, which was associated with reduced metabolism of energy, nucleotides, vitamins and glycans, and reduced biodegradation of xenobiotics (Montassier et al., 2014). Additionally, paclitaxel treatment in mice caused a decrease of *Firmicutes* phylum, consequently lowering SCFAs,

including butyrate, which was associated with increased levels of pro-inflammatory cytokine IL-1β and adverse effects such as decreased locomotion (Grant et al., 2021). Positive effects on neuropathy symptoms following sodium butyrate supplementation were also observed in animal models of obesity-induced peripheral neuropathy and neuropathy following chronic constriction injury (Bonomo et al., 2020; Kukkar et al., 2014). To date, only one study investigated sodium butyrate administration in CIPN. Jessup et al. demonstrated that sodium butyrate supplementation reduced paclitaxel-induced nociceptive hyperexcitability, thermal hyperalgesia, and cold allodynia (Jessup et al., 2023). The mechanisms underlying the positive effects of SCFA on CIPN remain unclear, but may involve the reduction of neuroinflammation, the reduction of proinflammatory cytokines levels, and the inhibition of proinflammatory macrophages and microglia via the inhibition of NF-κb (Caetano-Silva et al., 2023; Chang et al., 2014; Liu et al., 2012). The microbiome bacteria also produce polyphenolic derivates such as urolithin and secondary bile acids such as tauroursodeoxycholic acid. Although these metabolites had neuroprotective effects in animal models and clinical studies of neurodegenerative disorders such as autoimmune encephalomyelitis, Alzheimer's disease, Parkinson`s disease, and amyotrophic lateral sclerosis, the effects on CIPN are still unknown (Duan et al., 2002; Elia et al., 2016; Ramalho et al., 2006; Shen et al., 2021; Thams et al., 2019).

3.4. Bacterial Biomolecules and CIPN

Other biomolecules produced by the microbiome are enzymes, including β-glucuronidase, β-glucosidase, β-galactosidase, and nitroreductase. Bacterial enzymes contribute to the biotransformation of chemotherapy drugs, potentially impacting drug efficacy, dysbiosis, and adverse effects (Guthrie et al.; Westman et al., 2012). Although there is no direct evidence for the role of microbial enzymes in CIPN, these enzymes, besides being involved in drug metabolisms and degradation of natural food polymers such as complex carbohydrates, also assist with vitamin metabolism and intake. For example, vitamins from the B group, including biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine, are crucial for neuronal development and function and are synthetised by bacteria (Hill, 1997; Said et al., 1998; Said et al., 2001). These vitamins are then absorbed by enterocytes via transporters such as the sodium-dependent multivitamin transporter (SMVT,

SLC5A6) or the proton-coupled folate transporter (PCFT) or via passive diffusion (Prasad et al., 1999; Zhao et al., 2011). However, microbiome bacteria also use vitamins, such as vitamin B12, and chemotherapy-induced dysbiosis may lead to an increase in vitamin-consuming strains compared to vitamin-producing strains, contributing to vitamin B12 deficiency in cancer patients and the development of neuropathies (Degnan et al., 2014; Li et al., 2017; Lindenbaum et al., 1988; Molina et al., 2009; Schloss et al., 2017).

3.5. Bacterial neurotransmitters and CIPN

Intestinal bacteria also release neurotransmitters and neurotransmitter precursors, allowing the communication of the gut microbiome with the central and peripheral nervous systems. GABA and monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine are important signalling molecules allowing pain perception and processing in the central nervous system, and gabapentin (GABA analogue) or serotonin and norepinephrine reuptake inhibitors were used in clinical studies for the treatment of painful conditions, including CIPN, although with inconclusive results (Hershman et al., 2014; Rao et al., 2007). Currently, only duloxetine, a serotonin-norepinephrine reuptake inhibitor, is recommended for CIPN treatment by The American Society of Clinical Oncology (ASCO) (Hershman et al., 2014). Although it is not clear how chemotherapy drugs impact the signalling of these neurotransmitters, Chen at al., demonstrated that paclitaxel reduces GABA-induced membrane hyperpolarisation and causes a depolarising shift in the reversal potential of rat dorsal horn neurons, reducing spinal synaptic inhibition (Chen et al., 2014). Microbiome bacteria also produce neurotransmitter precursors, including tryptophan, indole, and indole derivates (Dehhaghi et al., 2019; Williams et al., 2014). Tryptophan is the sole precursor of serotonin, a neurotransmitter that regulates CNS and PNS function. The majority of host serotonin is produced using bacterially derived tryptophan by enterochromaffin cells in the intestine. Serotonin and tryptophan can be then released into the lamina propria and systemic blood, where they regulate the function of neurons, immune cells, and glial cells (Roth et al., 2021). Additionally, studies show that monoamine neurotransmitters, such as serotonin, dopamine, and norepinephrine, are involved in CIPN and monoamine reuptake inhibitors prevent CIPN development, underpinning the role of neurotransmitters in CIPN (Hache et al., 2015). However, a

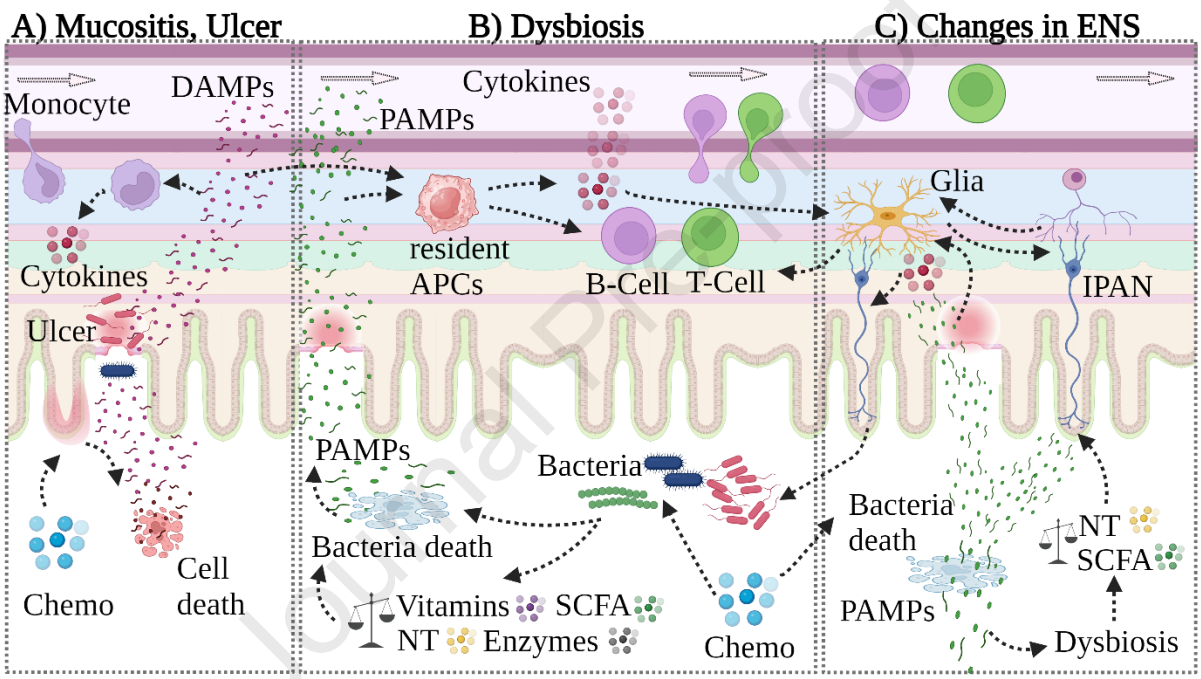
direct link between microbiome-derived tryptophan, monoamine synthesis and CIPN has not yet been established (for studies summary, see (Costa-Pereira et al., 2019; Mansooralavi et al., 2023; Micov et al., 2020; Omran et al., 2021)). A recent study also shows that bacterial indole directly activates nociceptor endings via TRPA1 (Chung et al., 2022).

3.6. Sex, microbiota composition, and CIPN

A direct link between sex, microbiota composition, and CIPN has not yet been established. Nonetheless, next to chemotherapy drugs, sex may also impact microbiome composition and possibly contributes to neuroinflammatory processes and variability in the above mentioned metabolites and, hence, to CIPN development (Cabanero et al., 2022; Lombardo et al., 2021; Zhang et al., 2021). For example, Zhang et al. sequenced the gut microbiomes of individuals of varying ages (26 to 76 years) and compared these with published datasets. Interestingly, the gut microbiota diversity of premenopausal women was higher compared to men. Specifically, the authors found higher abundances of species belonging to *Bacteroidetes (Bacteroides spp.)* and *Firmicutes (Clostridium, Eubacterium, and Ruminococcus)* in women compared to men (Zhang et al., 2021). These differences in the microbiome composition between sexes could be driven by sex hormones, such as estrogen and testosterone (reviewed in (Yoon & Kim, 2021)). On the other hand, the microbiome can also impact the metabolism of sex hormones. Specifically, gut bacteria produce glucuronidases, enzymes that are involved in the metabolism and reabsorption of sex hormones, including estrogen and testosterone (Collden et al., 2019; Flores et al., 2012). The variations in sex hormone metabolism could impact the neuroinflammatory processes contributing to CIPN pathology and possibly explain the sexual dimorphism seen in CIPN patients. Clinical and pre-clinical evidence provide evidence for sexual dimorphism in CIPN, and different studies consider sex differences as a risk factor for CIPN (reviewed in (Cabanero et al., 2022)). In general, women develop CIPN with higher incidence and experience increased severity of neuropathy symptoms compared to men (Meta-Analysis Group In et al., 1998; Trendowski et al., 2021; Unger et al., 2022). However, in one clinical study and preclinical models of paclitaxel or oxaliplatin-induced peripheral neuropathy, males developed more severe neuropathy compared to females (Davidson et al., 2019; McNeish et al., 2024; Warncke et al., 2021). On the other hand, in preclinical models of vincristine

461 or cisplatin-induced neuropathy, no differences between sexes were found (Nachnani et al., 2023;
462 Starobova et al., 2019). Considering the variability of the above findings, the effects of sex on the gut
463 microbiome, neuroinflammatory processes, and the function of peripheral nerves (and vice versa) are
464 also likely impacted by chemotherapy drugs and necessitate the consideration of environmental and
465 genetic factors and patient comorbidities. In summary, the relationship between sex, the microbiome,
466 and CIPN is currently unclear, and future studies addressing this association are necessary.

467



468

469 ***Figure 2.*** *Putative mechanisms of gastrointestinal microbiota contribution to inflammation.* ***(A)***
470 *Chemotherapy (Chemo) drives intestinal inflammation (mucositis) and causes damage to the epithelial*
471 *barrier (ulceration). Additionally, chemotherapy causes mucosal cell death, resulting in the release of*
472 *danger-associated molecular patterns (DAMPs). DAMPs then enter deeper layers of the*
473 *gastrointestinal (GI) tracts and the systemic circulation through damaged epithelium or ulceration.*
474 *Released DAMPs amplify the local inflammation by activating resident innate immune cells such as*
475 *macrophages or neutrophils to release pro-inflammatory cytokines and chemokines. This results in*
476 *infiltration of innate and adaptive immune cells, such as monocytes and lymphocytes, to the site of*
477 *inflammation and further cytokine and chemokine release.* ***(B)*** *Chemotherapy also alters the intestinal*

microbiota ratio, causing dysbiosis and bacterial cell death. This leads to the release of pathogen-associated molecular patterns (PAMPS), such as lipopolysaccharides and RNA/DNA fragments. PAMPS then penetrate lamina propria and submucosal layers of the GI tracts and enter the systemic circulation through the damaged epithelial barrier. Additionally, PAMPs in deeper layers of the GI tract activate resident antigen-presenting cells (APCs) to trigger adaptive immunity. T and B cells then migrate through the systemic circulation to lymphoid organs and initiate adaptive immune response, consequently amplifying inflammation. ***C)*** *Dysbiosis also affects the production of beneficial bacterial metabolites, such as bacteria-derived vitamins, short-chain fatty acids (SCFAs), and enzymes and leads to dysregulation in neurotransmitter (NT) production. This, in turn, is detected by interconnected intrinsic sensory neurons (IPAN) innervating mucosal epithelium and neurons of the submucosal and myenteric plexus of the ENS. Additionally, IPANs, ENS neurons and enteric glia may directly detect PAMPs via TLRs and activate enteric glial and resident immune cells to release pro-inflammatory cytokines, amplifying local inflammation and attracting more immune cells. (Adapted from (Zhang et al., 2022)).*

4. Targeting the microbiome for the treatment of CIPN

CIPN treatment continues to remain very challenging, as conventional therapeutic approaches for neuropathies and pain, such as the use of opioids, fail to manage CIPN symptoms and cause additional adverse effects such as constipation (Starobova & Vetter, 2017). Given the complex pathobiological processes contributing to CIPN, more unconventional approaches may need to be explored, including the use of microbiome modifying strategies, such as the use of probiotics, antibiotics, or faecal microbiota transplantation (FMT) (**Table 2**). These approaches aim to correct chemotherapy-induced dysbiosis and the consequent inflammatory processes and may positively affect CIPN development.

Probiotics - defined as “live microorganisms - when administered in adequate amounts confer a health benefit on the host” (Hill et al., 2014). Probiotics help to modulate the composition of the gut microbiome, assist in breaking down complex carbohydrates and fibres, and assist in production of essential vitamins and short-chain fatty acids (Corr et al., 2007; Hill, 1997; Larsbrink et al., 2014; Reichardt et al., 2014; Zyrek et al., 2007). Only few studies to date have investigated the effects of

505 probiotics in the context of CIPN (**Table 2**). For example, Cuozzo et al. tested the probiotic formulation
506 SLAB51 (Bonfili et al., 2020) for the prevention of paclitaxel-induced neuropathy and demonstrated a
507 reduction in mechanical and cold hyperalgesia in mice that received SLAB51. Additionally, the
508 supplementation of SLAB51 increased the expression of opioid and cannabinoid receptors in the spinal
509 cord, prevented nerve fibre damage in the skin and modulated serum proinflammatory cytokines
510 (Cuozzo et al., 2021). Although, these results are promising, the benefits of probiotics use for CIPN
511 treatment in patients remain unknown.

512 It is well established that oral administration of antibiotics modulates the composition of the gut
513 microbiome (Yang et al., 2021). However, how this contributes to the development of CIPN or how this
514 could be used for CIPN treatment is still unclear. To date, only few rodent studies have investigated the
515 effects of several antibiotics on the gut microbiome and CIPN (Ma et al., 2022; Shen et al., 2017; Shi
516 et al., 2023) (**Table 2**). For example, the eradication of the gut microbiome using oral administration of
517 ampicillin, neomycin, metronidazole, and vancomycin prior oxaliplatin administration resulted in
518 alleviation of oxaliplatin-induced mechanical hyperalgesia, and the reduction of the number of
519 macrophages and the release of proinflammatory cytokines in DRGs (**Table 2**). Minocycline, a second-
520 generation tetracycline, is the most studied antibiotic in context of CIPN. In several studies performed
521 in rodents, minocycline administration alleviated CIPN following chemotherapy drugs such as
522 vincristine, oxaliplatin or paclitaxel (Boyette-Davis & Dougherty, 2011; Boyette-Davis et al., 2011;
523 Robinson et al., 2014; Salat et al., 2019; Starobova et al., 2019), possibly via the inhibition of
524 inflammatory processes including the inhibition of TLR4 in microglia, astrocytes, or monocytes.
525 However, in these studies, minocycline was administered via intraperitoneal injections and therefore
526 the effects of minocycline on the gut microbiome in these studies and how this may have contributed
527 to the CIPN alleviation, is unknown. Only one clinical study investigated the effects of minocycline
528 oral administration on paclitaxel-induced neuropathy (Pachman et al., 2017) (**Table 2**). In this study,
529 minocycline significantly reduced the daily average pain score and fatigue, however, there were no
530 reports about the microbiome composition changes caused by minocycline. Therefore, it is not clear
531 whether the positive effect of oral minocycline on CIPN was mediated by its direct anti-inflammatory

effects, or by its effects on microbiome composition. However, in a study performed in rodents, oral minocycline specifically increased the abundance of *Lachnospiraceae* family and *Clostridiales* family XIII, in the gut microbiome (Schmidtner et al., 2019) that are associated with increased butyrate production. Although increased butyrate levels were associated with lower pain severity (Bonomo et al., 2020), the connection between increased butyrate production by these bacterial strains and neuropathy severity is still unclear.

Faecal microbiota transplantation (FMT) is a procedure in which the faeces from a healthy donor with a large variety of gut bacteria is transplanted into an recipient with dysbiosis to restore the healthy variety of the microbiome (Kim & Gluck, 2019). FMT has been previously used for the alleviation of irritable bowel syndrome (IBS)-induced abdominal pain (Johnsen et al., 2018). Additionally, FMT attenuated peripheral neuropathy and induced changes in peripheral nerve resident immune cell populations in obese mice that were fed a western diet (Bonomo et al., 2020). Only one study to date has investigated the effect of FMT on CIPN in rodents (Shi et al., 2023). This promising study showed that paclitaxel treatment caused microbiome dysbiosis, and induced mechanical allodynia and thermal hyperalgesia, which were alleviated following FMT. Additionally, FMT reduced the expression of TLR4, p-p38MAPK, and GFAP in the colon and spinal dorsal horn indicating reduction in glia cell activation (Shi et al., 2023). Although these results are promising, further studies are needed to understand the positive effects of FMT on CIPN.

Vitamin deficiency, such as vitamin D deficiency, is another factor that was previously connected to a higher risk of developing CIPN (Chen et al., 2023; Grim et al., 2017; Jennaro et al., 2020; Wang et al., 2016; Yildirim & Cengiz, 2020). However, the relationship between vitamin D deficiency, the gut microbiome and CIPN is not well understood (reviewed in (Gwathmey & Grogan, 2020)). Nonetheless, Vitamin D is known for its role in calcium homeostasis, and the vitamin D receptor (VDR) is linked to the development of chronic pain conditions, including peripheral neuropathies and visceral pain (Habib et al., 2020). The VDR is a member of the nuclear receptor superfamily, regulates gene expression and it is expressed in nearly all nucleated cells, including immune cells and peripheral and central neurons (Carlberg et al., 1993; Liao et al., 1990; Sone et al., 1991). The target genes of VDR include growth and

559 neurotrophic factor receptors (nerve growth factor receptor, epidermal growth factor receptor, GDNF
560 receptor) (Pertile et al., 2018; Riaz et al., 1999; Shen et al., 2011), ion channels (TRPV1,5 and 6) (Chen
561 et al., 2023; Chen et al., 2018; Long et al., 2020; Long et al., 2021; Taparia et al., 2006), endogenous
562 opioid receptor agonists (proopiomelanocortin, pro-dynorphin, pro-enkephalin) (Bazzani et al., 1984;
563 Poisbeau et al., 2019) and proteins involved in modulating neuronal axon growth and myelination
564 (Chabas et al., 2013). A systematic review that included rodent and human studies showed that Vitamin
565 D levels also influence the composition of the gut microbiome (Waterhouse et al., 2019). However, the
566 specific changes in the gut microbiome associated with vitamin D levels varied across those studies.
567 Therefore, vitamin D deficiency may contribute to CIPN by influencing the gut microbiome
568 composition, resulting in the activation of immune cells and the release of pro-algesic factors such as
569 cytokines and other signalling molecules as discussed above. Additionally, vitamin D deficiency may
570 directly impact pain perception and the function and regeneration of peripheral and central nerves.
571 However, a PubMed search (01/2024, chemotherapy AND neuropathy AND vitamin D) resulted in only
572 one clinical study that directly investigated the effects of vitamin D supplementation on CIPN
573 demonstrating that increased Vitamin D3 levels were associated with a decrease in CIPN severity
574 (**Table 2**). Most studies investigated the effects of vitamin D supplementation on diabetic neuropathy
575 with positive effects of vitamin D supplementation on neuropathy severity (Bell, 2012; Ghadiri-Anari
576 et al., 2019; Karonova et al., 2020; Lee & Chen, 2008; Shehab et al., 2012; Wei et al., 2020). However,
577 these studies were performed with a small number of patients and included a case report. On the other
578 hand, a large number of studies investigated the role of vitamin D in the regulation of the gut
579 microbiome and in the development of inflammatory diseases such as allergies, autoimmune diseases,
580 and inflammatory bowel diseases (Aggeletopoulou et al., 2023; Murdaca et al., 2021; Yamamoto &
581 Jorgensen, 2019). However, no studies to date have linked the effects of vitamin D supplementation,
582 microbiome changes, and CIPN directly.

583 Additionally, diets low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
584 (low FODMAP diet) and exercise are emerging microbiome-modulating interventions that could have
585 potentially positive effects on CIPN. Firstly, the low FODMAP diet is known to modulate the

586 composition of the gut microbiome, specifically reduction in *Bifidobacterium* (Cox et al., 2020; Sloan
587 et al., 2018; So et al., 2022). However, the low FODMAP diet has not yet been explored for the treatment
588 of CIPN. Nonetheless, several studies show reduced pain scores in fibromyalgia patients who follow
589 the low FODMAP diet (Black et al., 2022; Lowry et al., 2020; Marum et al., 2016). Although
590 fibromyalgia is not defined as neuropathy, there are some overlapping mechanisms with CIPN, such as
591 neuroinflammation (reviewed in (Sluka & Clauw, 2016)), that could be driving neuronal sensitisation,
592 raising the possibility of exploring the low FODMAP diet for CIPN treatment. Secondly, systematic
593 reviews and meta-analyses show positive effects of exercise on CIPN including effects of preventing,
594 mitigating, or improving CIPN symptoms (reviewed in (Brett Whalen et al., 2022) and (Tay et al.,
595 2022)). High-intensity exercise over longer periods of time also induced significant taxonomic and
596 metagenomic changes in gut microbiome, however, the mechanisms contributing to these changes are
597 currently unknown (Mailing et al., 2019). Similarly to low FODMAP diet, the direct connection
598 between exercise, gut microbiome changes, and CIPN has not yet been explored.

599 *Table 2: Summary of studies that investigated the therapeutic potential of microbiome modulation for*
600 *CIPN treatment. DRG: dorsal root ganglia; FMT: faecal microbiota transplantation; TLR4: toll-like*
601 *receptor 4; p-p38MAPK: phosphorylated p38 mitogen-activated protein kinase; GFAP: glial fibrillary*
602 *acidic protein.*

Therapy	Study Description	Species	Chemotherapy drugs	Outcomes	Ref.
Probiotics	Tested probiotic formulation, SLAB51, for the prevention of CIPN.	mouse	paclitaxel	-Prevention of mechanical and cold hypersensitivity. -Increased expression of opioid and cannabinoid receptors in the spinal cord.	(Cuozzo et al., 2021)

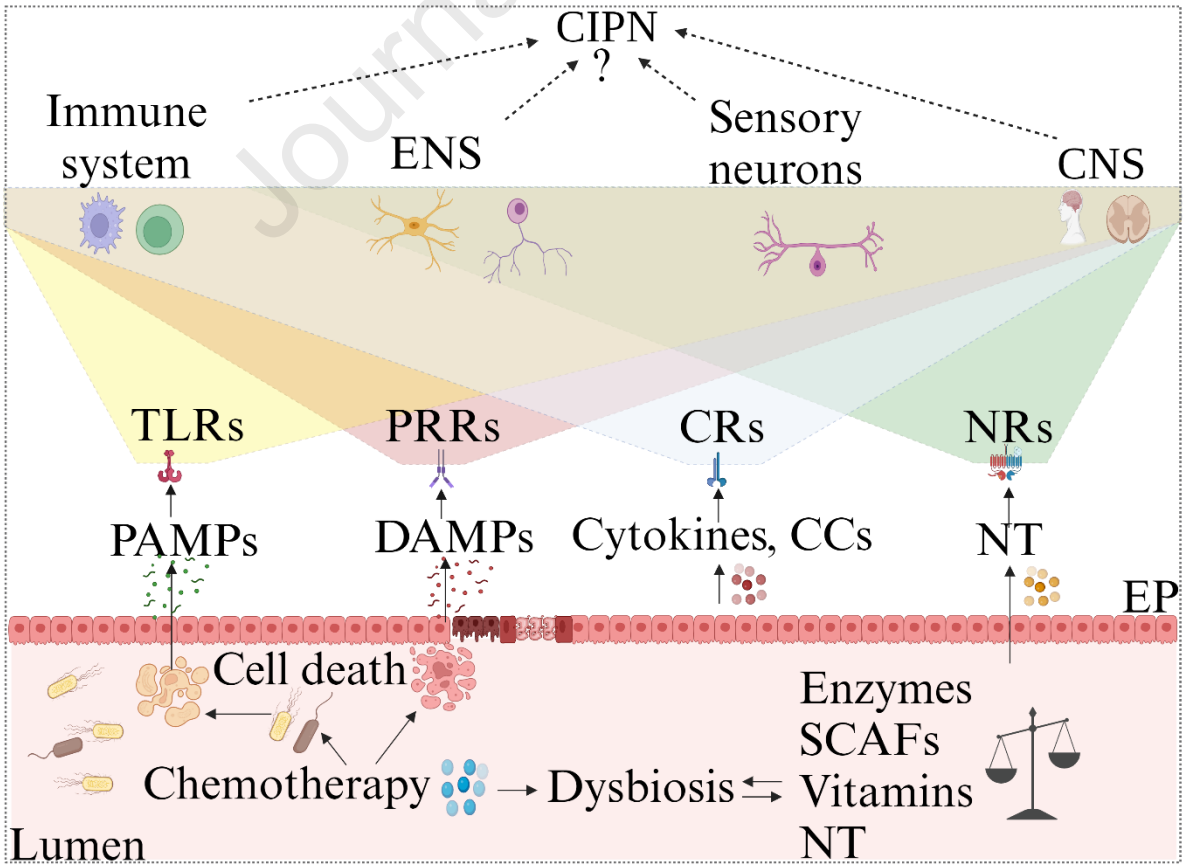
				-Prevention of nerve fibre damage. -Modulation of serum proinflammatory cytokines.	
Antibiotics	Tested orally administered antibiotics ampicillin, neomycin, metronidazole, and vancomycin for CIPN prevention.	mouse	oxaliplatin	-Feeding mice antibiotics reduced the diversity of microbiota. - Gut microbiota eradication prevented the development of oxaliplatin-induced mechanical hyperalgesia, the number of macrophages and the release of proinflammatory cytokines in DRGs.	(Shen et al., 2017)
	Tested orally administered antibiotics ampicillin, neomycin, metronidazole, and vancomycin for CIPN prevention.	mouse	oxaliplatin	-Gut microbiota depletion alleviated thermal hyperalgesia and mechanical allodynia. -Gut microbiota depletion also inhibited cytokine production in DRGs.	(Ma et al., 2022)
	Tested the effects of orally administered	rat	Paclitaxel	-No effect of gut microbiota depletion	(Shi et al.,

	antibiotics ampicillin, neomycin, metronidazole, and vancomycin on CIPN.			using antibiotics on CIPN severity.	2023)
	Tested the effects of Minocycline (oral, 2x daily) on CIPN	human	paclitaxel	-Minocycline significantly reduced the daily average pain score and fatigue. -No reports of microbiome diversity.	(Pachman et al., 2017)
FMT	Tested FMT for the prevention of CIPN	rat	paclitaxel	-FMT alleviated mechanical allodynia and thermal hyperalgesia -FMT reduced the expression of TLR4, p-p38MAPK, and GFAP in the colon and spinal dorsal horn.	(Shi et al., 2023)
Vitamin D	39 multiple myeloma patients with Vitamin D3 deficiency. Vitamin D3 supplementation for 6 months.	human	not specified	-Increased levels of Vitamin D3 were associated with a decrease in CIPN. -Unknown effect on gut microbiome.	(Oortgiesen et al., 2023)

603

604 **5. Conclusions:**

In conclusion, the contributions of the gut microbiome to inflammatory processes that may possibly drive CIPN development are not well understood, and this research niche is at its early stages. Nonetheless, few promising studies demonstrate the potential impact of chemotherapy-induced microbiome dysbiosis, leading to dysregulation of bacterial products, consequently impacting the function of neurons, immune and glial cells, and possibly contributing to CIPN development (**Figure 3**). However, these studies also raise many unanswered questions, such as to what extent inflammatory mediators and bacterial products produced as a result of microbiome dysbiosis actually contribute to neuronal sensitization and CIPN development, how these processes are impacted by, for example, sex, genetic and environmental factors and to what extend neuropathy and pain itself impact microbiome composition and hence the pathology of CIPN. Additionally, the majority of the studies were performed in rodents, and the benefits of microbiome-targeting strategies for patients suffering from CIPN remain elusive. Therefore, further studies are needed to fully understand how the microbiome contributes to inflammation driving CIPN and how we can use this knowledge for the development of effective treatments.



620 ***Figure 3**: Possible involvement of the gut microbiome in CIPN development. Chemotherapy-induced*
621 *dysbiosis and epithelial mucosal damage drive the dysregulation of vitamin, short-chain fatty acids*
622 *(SCFAs), enzyme, and neurotransmitter (NT) production and the release of pathogen and damage-*
623 *associated molecular patterns (PAMPs and DAMPs) following cell death and the release of cytokines*
624 *from resident immune cells. These chemical signals act upon their respective receptors, such as toll-*
625 *like receptors (TLRs), pathogen recognition receptors (PRRs), cytokine and chemokine (CCs) receptors*
626 *(CRs), and neurotransmitter receptors (NRs) expressed by a variety of cells, such as immune cells,*
627 *enteric neurons, enteric glia cells, sensory neurons, and the neurons and glia cells of the central nervous*
628 *systems possibly contributing to CIPN development and progression.*

629

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