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Neuroimmunological Manifestations of Chemotherapy Exposure: Implications for Mucositis, Glia and Cognition

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Abstract

Chemotherapy drugs reduce quality of life often causing acute and delayed central side-effects, termed Chemotherapy-Induced Cognitive Impairment (CICI). Another dose-limiting chemotherapy-induced side-effect is oral and intestinal mucositis which results in significant Gastrointestinal Tract (GIT) damage and intestinal inflammation. Recent interest has been paid to neurological complications arising in patients with gut disorders, yet little attention has been paid to the role GIT damage plays in CICI. Our current understanding of neuronal adaptations and behavioral consequences resulting from immune system dysregulation has paved the way for investigation into the neuroimmunological manifestations associated with chemotherapy. In a clinical setting cancer patients experience a cluster of symptoms, similar to that manifested in cytokine-induced sickness responses. Accordingly, it is suggested that peripheral inflammatory events, such as chemotherapy-induced mucositis, may indirectly cause glial dysregulation and potentiate cognitive changes in CICI. Perhaps it is time to examine the cancer experience in a multidisciplinary manner, in order to encapsulate the direct and indirect mechanisms underlying treatment-related side-effects. Specifically, understanding the neuroimmunological implications of chemotherapy-induced mucositis will provide further insight into the direct and indirect mechanisms underlying CICI pathogenesis.

Keywords: Chemotherapy-induced cognitive impairment; Chemotherapy-induced mucositis; Neuroimmune signalling pathways; Glial reactivity; Neuroinflammation; Microglia; Astrocytes

Abbreviations: CICCI: Chemotherapy-Induced Cognitive Impairment; GIT: Gastrointestinal Tract; CNS: Central Nervous System; IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome; ENS: Enteric Nervous System; UC: Ulcerative Colitis; CD: Crohn's Disease; IL: Interleukin; TNF: Tumour Necrosis Factor; BBB: Blood-Brain Barrier; EGCs: Enteric Glial Cells; TLRs: Toll-Like Receptors

Introduction

Chemotherapy drugs have proven invaluable in treating many cancers and improved the outcome for millions of cancer patients worldwide. Whilst the ultimate goal of chemotherapy is to prevent malignant cells from metastasizing, chemotherapy drugs are generally non-specific as they also target healthy, non-malignant cells. Chemotherapy induces a range of acute and delayed side-effects. In the Central Nervous System (CNS) the phenomenon is clinically recognized as CICI [1]. Peripherally, chemotherapy drugs negatively affect the GIT lining causing oral and/or intestinal mucositis. Although mucositis is an acute disorder which usually resolves upon treatment cessation, it is often a dose limiting side-effect due to the painful nature of the disorder [2,3]. Traditionally, these chemotherapy-induced side-effects have been considered to be separate disorders. However, recent evidence suggests that bidirectional communication pathways connecting the GIT and CNS may be implicated in the pathogenesis of both disorders. These pathways regulate a myriad of physiological and immune functions in health and various disease states manifesting from the periphery or centrally [4].

Peripheral inflammatory events or immune insults trigger a characteristic cluster of behavioural, cognitive, and affective changes, which are commonly referred to as cytokine-induced sickness responses [5,6]. Interestingly, many symptoms associated with cytokine-mediated sickness responses mimic the cognitive and behavioural changes commonly reported by chemotherapy recipients, including learning and memory dysfunction, fatigue and depression [7]. Cancer and chemotherapy exposure are associated with substantial immune dysregulation, involving inflammation [8], changes in cytokine levels [9] and mucositis which may be contributing to cognitive changes. Nonetheless, previous studies have failed to determine whether a link exists between these already established, yet disparate side-effects of chemotherapy. This review proposes that neuroimmune mechanisms and glial dysregulation may contribute to CICI symptoms both directly and indirectly via a peripherally driven inflammatory event: chemotherapy-induced mucositis.

As we unravel the complex aetiology of CICI, it soon becomes clear that the challenge in examining CICI lies within the cluster of symptoms cancer patients' experience. In a clinical setting, cancer patients reporting cognitive dysfunction often concurrently experience depression, anxiety, sleep deprivation, fatigue and pain [10-13]. Accordingly, Lee, et al. proposed a biological basis for cancer (and

cancer treatment) related symptom clusters; a cytokine-based neuroimmunological mechanism [14]. This concept stems from well-established studies which indicate that cytokine-induced sickness behaviours can be evoked by exposing animals to either infectious, inflammatory or certain pro-inflammatory cytokines [5,6]. Additionally, various gut disorders have been associated with psychological and cognitive comorbidities (reviewed below). From this it can be concluded that direct and indirect mechanisms may be contributing to cognitive changes observed in the chemotherapy setting. Neuroimmunological approaches in managing cancer and treatment-related side-effects may pave the way for novel and effective therapeutic and preventative approaches, ultimately improving the quality of life of cancer patients and survivors worldwide.

Gut disorders and cognition

CNS dysfunction has been recognised as a prominent feature in functional gut disorders, including Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) [15,16]. The idiopathic diseases comprising IBD include Ulcerative Colitis (UC) and Crohn's Disease (CD). UC usually involves the colon and ileum whereas CD mainly involves the rectum and colon. IBS, however, is currently viewed as being caused by dysregulation of the gut-brain axis. Whilst the symptomatology of both disorders includes pain, altered bowel movements and a host of physical, emotional, psychological and cognitive responses, IBD is strongly associated with intestinal inflammation unlike IBS.

The aetiology of functional gut disorders is complex and multifactorial, however it has been suggested and somewhat accepted that IBD and IBS may be triggered by psychological, environmental or physical stressors [17,18]. Consequently, several pathophysiological factors negatively affecting the gut-brain axis are pivotal to the disorders and include stress, chronic pain and immune activation [19,20]. Although a substantial body of literature exists, linking stress, chronic pain and immune activation to cognitive deficits, this area in the context of functional gut disorders has received little attention. Nonetheless, primary studies assessing these pathological factors in this patient population have shown deficits in specific aspects of cognition, such as verbal IQ [21]. In CD, regional morphological differences in cortical and subcortical structures have been critically linked to abdominal pain [22].

Psychopathological factors, such as depression and anxiety, are frequently observed to have effects in patients with functional gut disorders, and have been shown to play a role in cognitive deficits [23]. Approximately, 70% of patients with functional gut disorders experience some psychological comorbidity [24]. It is unclear as to which disease develops first, however it is well accepted that stress and anxiety is associated with IBS/IBD. Regardless of this, the impact of functional gut disorders on psychological processes is undeniable as the stress associated with symptom progression severely affects patients' quality of life. Taken into account, a biopsychosocial model has been proposed to clinically approach and conceptualize IBS pathophysiology [25]. This model encompasses a lifetime perspective from the patient's childhood through to their adult life integrating genetic, environmental, learning, stress and traumatic events. Fundamentally, it takes into account the interaction of the mind and emotions, the brain, the Enteric Nervous System (ENS) (discussed later) and the intestinal microenvironment, including food, the immune system and microbiota. Literature evidence demonstrates that functional gut disorders are strongly associated with a range of psychological comorbidities, specifically cognitive impairment; yet our understanding of the central consequences of other gut disorders, such as chemotherapy-related mucositis remains undetermined. Many chemotherapy drugs, such as Oxaliplatin and 5-Fluororuacil (5-FU) are responsible for inducing gut disorders and cognitive impairment, yet whether these comorbidities interact, remains to be elucidated.

Gut disorders caused by chemotherapy: mucositis

The pathogenesis of mucositis was defined in five phases by Sonis [2]. Mucosal barrier injury may occur throughout the entire GIT and result in oral and/or intestinal mucositis. The rapidly dividing epithelial layer lining the GIT is particularly prone to tissue injury from different chemotherapy drugs including 5-FU, methotrexate and cyclophosphamide. Consequently, apoptotic pathways are initiated in healthy mucosal tissue causing reduced cellular proliferation in the small intestine. Some hallmark characteristics of intestinal mucositis include villus atrophy, shallow crypts, inflammation and ulceration. Mucositis results in a heightened inflammatory response via the up-regulation and activation of various transcription factors, ultimately resulting in elevated circulating pro-inflammatory cytokines, in particular Interleukin-1 beta (IL-1β) and Tumour Necrosis Factor-alpha (TNF-α).

The most significant phase of mucositis for patients is during the ulceration phase as this involves loss of mucosal integrity. Painful ulcerating lesions in the GIT become susceptible to microbial infiltration and in severe cases can lead to bacteraemia and sepsis [2]. The clinical symptoms of mucositis generally begin five to ten days after chemotherapy treatment and include significant pain, abdominal bloating, nausea and vomiting, diarrhoea and constipation [26]. Although mucositis is an acute phenomenon which usually resolves once chemotherapy treatment has ceased, treatment may be prematurely ceased as a result of progressively worsening symptoms. Current guidelines for the prevention and management of mucositis fail to reveal effective treatment options [27]. Whilst mucositis pathogenesis is well understood, the indirect central effects of mucositis remain unknown. The complex neuroimmune axis has been suggested to be implicated in depression, a comorbidity of cancer diagnosis, and chemotherapy exposure [14]. Neurological manifestations from elevations in cytokine levels imply that neuroimmunological mechanisms underlying the pathogenesis of these chemotherapy-induced side-effects may be at play.

Cognitive changes following chemotherapy exposure

Although reports of cognitive decline in chemotherapy patients were functional magnetic resonance imaging and neuropsychological testing was observed in a group of breast cancer survivors who had received adjuvant chemotherapy treatment and was compared with a breast cancer control group who were not treated with chemotherapy [42]. E-date the 1980's, systematic research only commenced in the 1990's. Patients collectively termed the cognitive disturbances "chemobrain" or "chemofog" which heavily impacted daily functioning and quality of life, yet initial complaints were dismissed by doctors and the scientific community [7]. Previously, it was assumed that the brain was protected from systemically administered chemotherapy drugs by the Blood-Brain Barrier (BBB) and additionally, cognitive symptoms could be explained by the stress, anxiety and depression associated with cancer diagnosis. Extensive research in the recent years clearly indicate that many systemically administered chemotherapy drugs readily cross the BBB inducing structural, molecular and cellular

changes that impact upon cognitive function (see review 1) [1]. Mechanisms underlying the pathogenesis of CICI remain to be elucidated although suggestions include hippocampal damage and immune dysregulation (discussed below). In order to better understand the suggested mechanisms, it is important to review the clinical evidence and understand the negative impact imposed upon patients.

Clinical evidence of CICI

The main cognitive domains affected by CICI are executive functioning, attention and concentration, processing speed, reaction time, motor speed and dexterity [1]. Whilst current estimates of CICI prevalence differ greatly (14-85%), the worldwide prediction of cancer incidence reaching 70 million in 2020 highlights the need for continued research [28]. Consequently, the estimate of high survivability rates for many cancers results in increased survivor numbers and in turn, we will see an increase in the incidence of post-treatment issues [29]. Those affected by CICI experience stressors in many facets of their lives, including relationships (familial, friends and colleagues), employment, self-esteem/worth and finances; leading to a reduced quality of life. CICI patients commonly expressed frustration in having difficulty with simple tasks, such as remembering names, misplacing everyday items and trouble finding common words [30,31]. Emotions regularly described by CICI patients included distress, anxiety, frustration, irritability, depression and embarrassment [30-33]. Many summed up their feelings by describing as if they "felt stupid" or were "going crazy" and sometimes related their memory disturbances to the fear of being at risk for early dementia or Alzheimer's disease [30,34]. This evidence collectively supports the negative impact of CICI on patients and emphasizes the increased amount of efforts and time required to complete everyday tasks.

Breast cancer cohorts and duration of cognitive effects

Whilst the majority of CICI studies focus on breast cancer populations, cognitive deficits in a range of cancer types have been investigated, including myeloma, testicular and ovarian cancer [35-37]. Nonetheless, breast cancer populations offer researchers completion of extensive retrospective studies due to their typically good prognosis, allowing for more thorough evaluations of parallel short- and long-term sequelae [38-40]. The duration of cognitive changes is of particular interest to patients and for this reason, continues to be an area of much research. There is considerable variability surrounding the duration of chemotherapy-induced cognitive deficits or even existence of the phenomenon. Majority of the studies report improvement in cognitive symptoms after a period of time, yet some studies have indicated the presence of symptoms for ten-twenty years after treatment cessation [41-43]. Functional magnetic resonance imaging and neuropsychological testing was observed in a group of breast cancer survivors who had received adjuvant chemotherapy treatment and was compared with a breast cancer control group who were not treated with chemotherapy [42]. The chemotherapy group demonstrated hyporesponsiveness in executive functioning tasks performed 10 years post treatment, indicating significant long-term cognitive impairments when compared to the non-chemotherapy control group.

Neuroimaging studies have identified structural and molecular changes associated with chemotherapy treatment. Reductions in specific brain regions, such as frontal cortex, temporal lobes and cerebellar grey matter regions have been reported in breast cancer patients [44]. These reductions were evident for twelve months post-chemotherapy cessation yet improvements were reported in most regions four years later. Global brain networks become re-organized under chemotherapy treatment and thus, indicate a reduced ability for information processing [45]. Additionally, chemotherapy-induced white matter tract alterations may be interpreted as demyelination or axonal damage [46].

Animal models of CICI

Animal studies have confirmed that central structural and molecular changes may be accountable for the cognitive domains affected by common chemotherapy drugs. Several studies in rodents report declines in abilities to perform behavioural tasks following single drug administration of many chemotherapy drugs, including 5-FU, methotrexate and oxaliplatin [47-49]. Rodent behavioural tests have been adopted to understand the central pathological changes following systemic chemotherapy exposure, such as fear conditioning, novel object recognition and the Morris Water maze. These behavioural adaptations may be interpreted as hippocampal and frontal cortex region alterations which importantly, overlap with the brain structures implicated in CICI [1].

Specific CNS cell populations are sensitive to a range of chemotherapy drugs. One of the most widely reported central changes following chemotherapy exposure is reduced hippocampal cellular proliferation. This has been documented to occur with cyclophosphamide, methotrexate, thioTEPA and 5-FU [50-52]. These CICI animal models suggested that the hippocampal changes were associated with the hippocampal-dependent behavioural changes and memory deficits. Although cyclophosphamide most frequently reports cognitive changes and cellular alterations, negative findings on long-term hippocampal changes have also been reported [53]. Nonetheless, stem cells of the dentate gyrus are particularly susceptible to chemotherapy toxicity [54-56]. This is important to note as neurogenesis within the dentate gyrus is responsible for the proliferation and division of neural stem cells that form into new neurons or astrocytes, playing a pivotal role in hippocampal circuit plasticity and memory consolidation [57,58]. Consistent with patient observations of leukoencephalopathies and white matter tract lesions, animal and *in vitro* studies have shown that both mature oligodendrocytes and their precursors may be susceptible to the action of chemotherapy drugs [1]. Whilst there is clear evidence that specific central cell populations are susceptible to reductions in cellular proliferation following chemotherapy exposure, some studies have reported no changes [59,60]. This evidence reflects the complex aetiology of CICI, indicating various structural, molecular and cellular changes contributing to cognitive impairment following chemotherapy exposure. The aforementioned studies fail to take into account neuroimmune mechanisms that may be at play, whether directly or indirectly. Perhaps it is time to consider the impact other chemotherapy-induced peripheral inflammatory events may be having on CICI, such as immune challenges in the context of malignant tissues, more specifically gut toxicities, such as mucositis.

The contradiction: host immunity, dysregulation and cancer

The ultimate goal of the immune system is to protect and defend the host from infection and insults by recognizing, repelling and eliminating pathogens and foreign molecules. Further, inflammation is an essential defensive response resulting in physiological processes critical in host healing. The toll that both malignancies and

chemotherapy treatments have on the host is particularly enigmatic in the context of the immune system, whereby complex inflammatory processes contradict and manipulate responses; a dynamic network that primarily ensures protection against foreign pathogens whilst remaining tolerant of self-antigens. This somewhat contradictory phenomenon results in immune dysregulation which in turn, may result in central effects via the neuroimmune interface and signalling pathways.

Inflammatory processes become dysregulated in cancer and anti-cancer treatments. On one hand, endogenous immune processes and inflammatory cascades attempt to eliminate malignant cells from the host. Yet, simultaneously within malignant cells, similar pathways are initiated and inflammatory signalling molecules contribute to cancer establishment and progression. Several lines of evidence have suggested inflammatory processes are the seventh hallmark for cancer establishment and progression [8,61,62]. To further complicate matters, chemotherapy treatments are associated with increased circulating inflammatory markers, yet suppression of immune activity is commonly reported (discussed below). It is well established that immune dysregulation occurs in several disorders negatively affecting the CNS and in some cases, the gut. To illustrate this point, a few disorders, such as neuropathic pain will now be further discussed.

Immune dysregulation in animal models

Several convergent lines of experimental and clinical evidence have supported the hypothesis that pro-inflammatory cytokines are pivotal in the pathophysiology of not only cancer-related and anti-cancer treatment-induced symptoms, but other disorders, including chronic fatigue syndrome, neuropathic pain and major depression. Elevated circulating pro-inflammatory cytokines, such as (IL-1) and (TNF-α) have been reported in clinical studies examining chronic fatigue syndrome, major depression and various pain states [63,64]. IL-1 action is regulated by a complex network of molecules and is a potent stimulus of corticotrophin-releasing hormone, activating the hypothalamic-pituitary-adrenal axis, an important stress hormone which has been well documented in major depression [63]. Additionally, TNF-α is widely recognised as an important factor in the mediation of major depression, chronic fatigue syndrome and neuropathic pain [63-65]. Rodent models have reported that intraperitoneal administration of TNF-α results in dose dependent pain responsivity, indicative of hyperalgesia (heightened sensitivity to pain) [66]. The hippocampus is associated with pain perception and cognition [67] and accordingly, a rat model of chronic constriction injury of the sciatic nerve reported increased hippocampal TNF-α levels [65]. These studies indeed demonstrate a pivotal role for the aforementioned pro-inflammatory cytokines in the pathogenesis of a range of disorders and disease states. It should be noted that the disorders mentioned in this section also often occur simultaneously in cancer patients undergoing chemotherapy treatment.

Immune dysregulation in cancer and chemotherapy

There is growing consensus on two recognized interactions between cancer and the immune system. Firstly, host immunity has the ability to recognize and reject malignant cells and immuno-surveillance can prevent tumour development and control recurrence. Consequently, activation of the innate immune system leads to the production of highly immuno-stimulatory cytokines, systemic inflammation and T-cell and B-cell activation, with the goal of eliminating malignant cells. Secondly, many inflammatory mediators and cells involved in detecting and eliminating malignancies also play a key role in the migration, invasion and metastasis of malignant cells, thus promoting tumour expansion [68,69]. This double edged sword results in a plethora of intertwined and complex interactions in which the immune system recognizes and tries to reject tumour formations whilst inflammatory processes simultaneously enable tumour progression and development.

Additionally, chemotherapy drugs also induce inflammatory responses which may be either local, around the site of administration or systemic in nature resulting in mucositis. Several chemotherapy drugs including 5-FU (anti-metabolite), etoposide (topoisomerase II inhibitor) and doxorubicin (anthracycline) elevate pro-inflammatory cytokine production *in vitro* [70]. Importantly, this demonstrates that most cytotoxic anti-cancer drugs, regardless of their mechanism of action, increase circulating cytokines. Such findings have been translated into clinical studies linking circulating pro-inflammatory cytokine elevations with common chemotherapy-induced side-effects, such as fatigue, depression, pain and cognitive impairment [71,72]. Extensive studies revealed the importance of elevated circulating pro-inflammatory cytokines in sickness responses which often result in cognitive changes and interestingly, mimic CICI reports. Finding therapeutic approaches that target the immune system has the potential to improve multiple chemotherapy-related side-effects which all have an immune component to their aetiology.

The intimate bidirectional relationship shared between the CNS and the GIT presents as a potential mechanism that may contribute to CICI symptom severities. As such, it is plausible that chemotherapy-induced peripheral inflammatory events, such as mucositis, may trigger central cell population changes. Peripheral-to-central changes occurring via neuroimmunological pathways may result in behavioural (cognitive) changes, similar to those apparent in cytokine-induced sickness responses [5,73,74]. Although a cytokine-based neuroimmunological mechanism of cancer-related symptoms has been suggested [14], CICI researchers are yet to examine the indirect central effects of chemotherapy-induced peripheral inflammatory events, such as mucositis.

"Little brain" to "big brain" inflammation and signalling pathways

The ability of the ENS to self-regulate (hence "little brain") and act similarly to the CNS ("big brain") makes it the largest and most complex division of the peripheral nervous system [75]. Previous literature has suggested that the GIT is a vulnerable passageway through which pathogens may influence the CNS and lead to abnormalities, for example, neuroinflammation contributing to autism [76] and multiple sclerosis [77]. A well-established link exists between various neurodegenerative diseases and the role neuroinflammation plays in their pathogenesis [78,79]. However, few studies have examined the influence of peripheral-to-central immune signalling and neuroinflammation in the context of chemotherapy- induced mucositis and CICI.

Inflammation in the "little brain": ENS inflammation

The ENS contains more than 400-600 million neurons [80] and an extensive network of Enteric Glial Cells (EGCs). Although EGCs support enteric neurons, the precise mechanisms by which EGCs support enteric neurons remains to be fully elucidated. EGCs share similarities with their CNS counterparts, astrocytes in morphological,

functional and even molecular capabilities [81]. As well as exerting protective functions, EGCs are key players of the ENS during intestinal inflammation and immune responses. Their intimate relationship with enteric neurons and their responsiveness to local inflammation makes them a prime target for therapeutic intervention as has been investigated in the CNS with targeting glial cells.

From our understanding of the intimate bidirectional relationship shared between the GIT and the CNS, it is not surprising that a diverse range of neurodegenerative diseases arise from systemic infections and inflammation, such as multiple sclerosis and Alzheimer's disease [76,82]. We have all experienced the change in mood, emotion and cognition when one is faced with systemic infection, a cold or influenza. Numerous reports indicate that this immune response is driven by a dialogue between the peripheral systemic infection and our brain [73]. The gastrointestinal immune system is considered the primary immune organ of the body as it induces and maintains peripheral immune tolerance. This is achieved via complex cellular networks with specialized immuno-regulatory functions, including interactions between the microbiota and host. Impaired host immune defenses and mutations in pattern recognition receptors lead to GIT dysfunction and enables invasion of pathogens [83]. The downstream effect of such events results in chronic GIT inflammation and/or dysbiosis (a loss of control of local immune responses resulting in an unbalanced enteric microbiota) having substantial implications in the pathogenesis of rheumatoid arthritis, IBD and asthma [84-86]. From this evidence it is clear that GIT inflammatory events may modify central processes controlling behaviour and aligns with our central hypothesis that chemotherapy-induced mucositis may result in central changes via neuroimmune mechanisms involving glia, discussed in more detail below.

Glia: the "other brain"

Glial cells are critical in brain development, function and plasticity in both health and disease and fall into three cell types; astrocytes, microglia and oligodendrocytes. Neurons, astrocytes and oligodendrocytes arise from neural progenitor cells whilst microglial cells originate from peripheral macrophage cell lines [87]. Glia perform a host of regulatory functions within the CNS, from supporting neurons and regulating synaptic neurotransmission, to maintaining calcium homeostasis and clearing intracellular ions and neurotransmitters [88]. A bidirectional communication occurs between neurons and glia (astrocytes and microglia) which is now widely accepted as the neuroimmune interface; the tripartite and tetrapartite synapse describes this complex intertwined relationship in health and disease [89,90].

Glia plays a vital role in various aspects of brain function. The ambiguities of glial cells in health go far beyond our current understanding and deserve much more attention. An area of particular interest is the mechanism by which these central immune cells are involved in the pathogenesis of CNS disease states. Several researchers have gained valuable insight to this question and begun to unravel the mechanisms by which glia contributes to the pathogenesis of neurological and neurodegenerative diseases, such as Alzheimer's disease, neuropathic pain, ischaemia and migraine. The common thread linking these diseases is glial priming and subsequent neuroinflammation.

"Big brain" inflammation

Microglia and astrocytes may become reactive or primed either from direct-central insults or indirect-peripheral inflammatory events triggering neuroinflammatory responses. Microglia is highly sensitive to insults so are the first to react, unlike astrocytes which respond more slowly and in a more controlled manner [88]. In their reactive states, both glial cell types undergo morphological changes augmenting a cascade of detrimental functional outcomes leading to tissue damage and neuronal death [91]. In particular, reactive glia overproduce prostaglandins, pro-inflammatory cytokines, chemokines, mediators and reactive oxygen and nitrogen species having detrimental effects on neuronal function and survival via oxidative stress [92]. Primed glia reduces output of anti-inflammatory molecules, decrease neurotrophic support, dysregulate calcium, glutamate and brain derived neurotrophic factor resulting in excitotoxicity and neuroinflammation [93]. Interestingly, both cell types may remain in a primed state whereby they continue to be sensitized after the initial stimulus has resolved. Although primed glia appears active due to their morphological form, they do not overproduce inflammatory mediators until challenged, whereby they react quickly and elicit an exaggerated immune response [94]. In particular brain regions this may influence behaviours involving cognition [89,95].

Glia modulates neurotransmission and cause neuronal injury via various mechanisms including a reduced ability to produce neurotrophic support, excitotoxic glutamate-receptor mediated damage and oxidative stress [96]. Glutamate is the primary excitatory neurotransmitter instrumental in neuronal plasticity and thus, key in learning and memory consolidation [97]. The glutamate transporters GLAST and GLT-1 are localized on astrocyte membranes [98]. Reactive astrocytes undergo reduced expression of glutamate transporters and lose their ability to re-uptake glutamate, yet continue to release glutamate into the synapse [99,100]. Additionally, reactive astrocytes inhibit production of glutamine synthetase, an enzyme that converts extracellular glutamate to glutamine, vital in neuroprotection [101]. From this, it is not difficult to see that a significant feature of many neurodegenerative disorders is reactive or primed glia, and subsequent neuroinflammation. In the context of chemotherapy exposure, inflammation (central or peripheral) occurring via either direct or indirect mechanisms may trigger glial dysregulation and neuronal consequences, impacting negatively on cognition.

The host immune system utilises innate immune signalling to recognise microorganisms, detected by molecular structures shared by a large number of pathogens; exogenous Microbe-Associated Molecular Patterns (MAMPs) and endogenous molecules Danger-Associated Molecular Patterns (DAMPs). Toll-Like Receptors (TLRs) represent a class of innate immune receptors belonging to the IL-1/TLR superfamily and act as pattern recognition receptors capable of responding to MAMPs, DAMPs and more recently, Xenobiotics-Associated Molecular Patterns (XAMPs) [102]. XAMPs represent foreign chemicals that include alcohol, methamphetamine and cocaine [103]. The mechanism by which XAMPs modify glial expression levels and morphology via TLRs may then present as a plausible mechanism contributing to CICI.

Although reactive glia might start as a beneficial process responding to an insult (disease, trauma, infection or drug exposure), it may, depending on the nature, duration and intensity of the insult, turn to a detrimental neuroinflammatory state. Defining neuroinflammation is by no means a simple task; however, it is generally accepted to include microglial and astrocyte reactivity and increased expression of pro-

inflammatory cytokines and chemokines [104]. Chronic neuroinflammatory states are known to contribute to neuronal loss and central homeostatic disturbances. It is widely accepted that systemic inflammation influences brain function and behaviours. The last two decades have revealed the pivotal roles microglia, astrocytes and neuroinflammation play in various neurodegenerative diseases. In addition to neurodegenerative diseases and central injuries, neuroinflammation has also been implicated in neuropathic pain, schizophrenia, epilepsy and perhaps most recently, cancer and cognitive decline following chemotherapy exposure [105-109]. Of particular interest to this review, is the potential for chemotherapy drugs to influence glial cell populations in both the brain and the spinal cord, having implications in cognition and pain pathways. Various chemotherapy drugs appear to be causing a generalized glial response which is not limited to specific drug classes [108-110]. These studies primarily focused on the direct-central effects of chemotherapy exposure, not accounting for the potential of GIT damage to indirectly exacerbate central changes via neuroimmune pathways. Peripheral-to-central immune signalling pathways offer a potential way in which peripheral inflammatory events, such as mucositis may be implicated in CICI.

"Little brain" to "big brain" signalling

Histories of abuse, life stressors and other psychological factors have been shown to play an important role in the onset of various functional bowel disorders [111,112]. As information is relayed in a bidirectional manner between the gut and the brain, it makes sense that the CNS may be modified by gut dysregulation. Information from the "little brain" to the "big brain" may be relayed via afferent neurons connecting the gut to the CNS. Pathways responsible for the transmission of various endocrine, neuronal, paracrine and humoral signals are vagal, humoral or neural. The vagus nerve provides a cytokine responsive neural pathway indirectly triggering the brain via afferent vagal input or leaky circumventricular organs [113].

Peripheral immune messages such as locally produced pro-inflammatory cytokines may travel indirectly to the CNS via neural signalling pathways, including but not exclusive to the vagus nerve [74]. Information detected by primary afferent neurons is transduced into a neural message which is then relayed to higher order brain regions. In the brain parenchyma this message is then re-transduced back into an immune message where locally produced cytokines alter brain function by acting either directly or indirectly on neurons or glia. In specific brain regions, this may result in behavioural adaptations, involving cognition and mood. Alternatively, the slower and more direct humoral pathway occurring at leaky circumventricular organs involves molecular intermediates, such as prostaglandins. Local inflammation activates peripheral tissue macrophages to increase release of pro-inflammatory cytokines, such as IL-1β and TNF-α. Consequently, macrophages and endothelial cells release chemokines and adhesion molecules that attract leukocytes [74]. As well as their essential roles in peripheral inflammation, circulating IL-1β and TNF-α are also key initiators of neuroinflammation. From this knowledge, we present these immune-to-brain signalling pathways as potential mechanisms by which chemotherapy-induced intestinal inflammation may directly and indirectly lead to neuroinflammation and glial dysregulation. Pro-inflammatory cytokines and mediators expressed during the pathogenesis of chemotherapy-induced mucositis may access the CNS via leaky circumventricular organs resulting in a neuroinflammatory response.

What the future holds

In the year 2020 it is estimated that 70 million cancer survivors will be disease free [7,28]. Nonetheless, a substantial proportion of survivors will have experienced either acute or delayed cognitive deficits during or post treatment cessation. Therefore, it is of paramount importance to consider the direct and indirect mechanisms underlying CICI to develop new strategies and treatments that will improve the quality of life of cancer survivors. To date, CICI animal models have failed to consider the impact of peripheral inflammatory responses on cognitive deficits. In fact, in most CICI animal studies, it is almost unquestionable that mucositis tissue damage would have certainly been present, yet these organs were not analysed. This limited angle of analysis may be missing incidental, yet crucial mechanisms in the aetiology of CICI. Irrespective of this, we acknowledge the many challenges faced by researchers undertaking CICI studies and teasing apart both the direct and indirect mechanisms presents with its own myriad of complications. Perhaps now is the time to examine chemotherapy-induced side-effects which more accurately reflect a clinical setting; elucidating how multiple chemotherapy side-effects work in unison.

One might argue that in general, the two major areas of the human body which become dysregulated following chemotherapy exposure are the gut and CNS; the "little" and "big" brains. The above sections clearly illustrate the recent substantial increase in literature implying that brain function is somewhat dependent upon gut function and vice versa. Many questions still remain and research should continue to clarify how the neuroimmune interface and signalling pathways may be implicated in CICI. The literature reviewed presents our theory that chemotherapy-induced intestinal inflammation may drive glial dysregulation via direct and indirect neuroimmune signalling pathways which may ultimately, potentiate cognitive impairment. Harnessing our understanding of these mechanisms and outlining ways in which the gut can modulate brain function and behaviours via neuroimmune signalling pathways may guide us to novel treatment approaches that encapsulate more targeted therapies aimed at treating multiple side-effects of chemotherapy treatment.

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Submission declaration

The authors hereby declare that this work has not been previously published (except in the form of an abstract for conference presentation), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder. No funding sources were utilized to produce this manuscript.

Conflict of Interest

The authors wish to acknowledge no conflict of interest.

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