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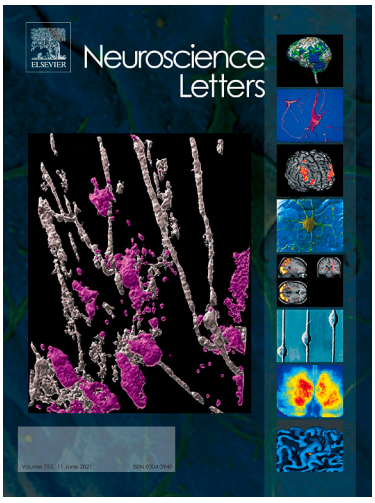

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Mini-Review: Aplastic Myelin Following Chemotherapy

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Abbreviations: oligodendrocyte precursor cell OPC, cancer therapy-related cognitive impairment CRCI, myelin basic protein MBP, brain derived neurotrophic factor BDNF, 5-Fluorouracil 5-FU, Methotrexate MTX, acute lymphoblastic leukemia ALL.

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Abstract:
The contribution of chemotherapy to improved outcomes for cancer patients is unquestionable. Yet as its applications broaden, so do the concerns for the long-term implications of chemotherapy on the health of cancer survivors, with chemotherapy-related cognitive impairment as a cause for particular urgency. In this mini review, we explore myelin aplasticity following chemotherapy, discussing the role of myelin plasticity in healthy cognition and failure of myelin plasticity chiefly due microenvironmental aberrations in chemotherapy-related cognitive impairment. Possible therapeutic strategies to mitigate chemotherapy-induced myelin dysfunction are also discussed.

I. Introduction

Owing to the advances in cancer diagnosis and treatment, the 5-year survival rate for all cancers has improved in the United States by over 30% with 2.6 million cancer deaths averted during 1991-2016 [1]. Chemotherapy accounts for a considerable part of this progress, especially for patients with late-stage disease. As a consequence of this progress, an increasing number of cancer survivors are burdened with the long-term consequences of chemotherapy, notably the syndrome of chemotherapy-related cognitive impairment (CRCI). CRCI, encompassed by the colloquial terms 'chemo-brain' or 'chemo-fog', is characterized by impaired attention, concentration, memory, processing speed and ability to multi-task and is described in a series of excellent reviews[2–4]. While cancer-related cognitive impairment involves many factors, including in some cases the effects of the cancer itself, in this review we will focus on the effects of chemotherapy specifically. Similar to but typically less severe than the neurological dysfunction induced by radiation therapy[5], chemotherapy-related cognitive impairment nevertheless can significantly diminish patient quality of life. Along with the several known mechanisms of chemotherapy-related cognitive impairment (neuroinflammation, impaired neurogenesis, aberrant synaptic pruning), white matter dysfunction is an important piece of the puzzle. While severe white matter compromise reflecting axonal injury and/or myelin loss can occur, commonly a more subtle dysregulation of white matter form and function is evident in advanced neuroimaging studies [6,7] (summarized in table 1). This dysfunction of myelin homeostasis and plasticity will be the focus of this review, drawing upon clinical evidence where possible and largely focused on preclinical studies.

The pathophysiological effects of chemotherapy and severity of chemotherapy-related cognitive impairment varies substantially depending on the cancer type, patient's age at diagnosis, and the different chemotherapy regimens used. Antimetabolite chemotherapeutic agents are particularly associated with neurotoxicity and cognitive impairment [8–12]. Various neurocognitive domains are impacted, including but not limited to attention[7,13], memory[7,14–16], processing speed[7,15,17,18], and executive function[19]. Certain genetic variants, such as *BDNF* polymorphisms, appear to predispose patients to more severe neurological dysfunction following chemotherapy[20–23].

The ample evidence from animal models and some human studies indicates that oligodendroglial lineage cells are significantly dysregulated by chemotherapy exposure, as are other elements of the brain microenvironment. In this review, we will examine the dynamics of myelination of the CNS and how this is impacted by systemic administration of commonly used

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chemotherapy agents. Understanding the interaction between developmental, homeostatic and adaptive myelination and the direct and indirect mechanisms of action of chemotherapeutic drugs will guide the discovery of therapeutic strategies for addressing chemotherapy-related cognitive impairment. Some of the plausible strategies, along with those already being tested in animal models or clinical trials, will be discussed here.

II. Oligodendrogenesis and myelination

Myelination is a major stepping stone in the evolution of the vertebrate nervous system. The highly efficient saltatory conduction of neuronal impulses, along with the metabolic support that axons receive from myelinating oligodendrocytes, are essential for the complexity of neurological functions humans rely on to interact with their environment[24–26].

Myelination and oligodendrocyte lineage dynamics throughout lifetime. Cortical and subcortical white matter myelination begins around the time of birth and continues throughout adult life. The period of developmental myelination extends through the third decade of life, and then myelin continues to accumulate in the neocortex and cortical projections, with the highest white matter volume observed during the 5th decade of life. [27,28]. Developmental myelination in childhood and adolescence follows predictable chronological and topographical patterns such that primary motor and sensory circuits are myelinated predominantly in the first decade of life, while associative cortices and their projections do so up through late adolescence and early adulthood. Consequently, disruption of myelination at different ages can confer different degrees of neurological dysfunction and cancer therapies in young children tend to cause more lasting neurological sequelae. Some areas like cingulate and frontal cortex remain incompletely myelinated in humans throughout life[28], suggesting continued opportunity for plasticity of myelin in these regions. DTI studies[29] and rodent models[30] illustrate that the frontal-temporal regions are last to mature[29]. Notably, and as will be elaborated further in the later sections of this review, the frontal-temporal regions of the brain are most vulnerable to chemotherapy-induced myelin deficits, and the complex cognitive functions often impaired after chemotherapy chiefly localize to these regions.

Our understanding of the mechanisms that underlie ongoing myelination throughout life is critical for predicting the influence of commonly used chemotherapy regimens. Myelin of the CNS is formed by oligodendrocytes. The pool of oligodendrocyte precursor cells (OPCs) is distributed throughout the nervous system and is considered the principal source of mature myelinating oligodendrocytes. Overall, the coalescing evidence suggests that oligodendrocyte lineage pool remains dynamic throughout life with adult OPCs continuing to proliferate, differentiate into functional oligodendrocytes, and form myelin[31–37], yet there may be some differences between rodents and humans, and between humans across the age span[32,38,39].

Myelination in the context of neural activity. Although the protracted period of myelination over the lifetime offers an opportunity for experience-dependent plasticity, there are activity-independent aspects of myelination. Indeed, myelin will form even around inert fibers in a dish, with its parameters defined by the physical constraints of the microenvironment along an axon [40], the axon caliber [41,42] and the regional identities of the OPCs that contribute to it [43].

On the backdrop of activity-independent myelination is a second mode of myelination, driven by neuronal activity. Even developmental myelination, in the past regarded as largely activity-independent, is also at least in part guided by the ‘use it or lose it’ principle. After the initial axon ensheathment, oligodendrocyte processes are either extended or retracted. The decision

between the latter two is driven by the activity of the neuron being wrapped. This model was first outlined in a zebrafish model, where silencing neuronal activity decreases the number myelin sheets formed by an individual oligodendrocyte [44] and impairs selection of axons for myelination[45], both via decrease in activity-dependent vesicular secretion.

Several lines of evidence also support activity-driven myelination in adult rodents. The roles of activity-regulated myelination have been well-studied in motor circuitry, where cortical projection neuronal activity regulates oligodendrocyte lineage cells and myelin architecture [46–48]. The oligodendrocyte lineage pool (oligodendrocyte precursor cells (OPCs) and earlier pre-OPCs) is acutely sensitive to motor learning, with new oligodendrocytes forming as early as 2.5 hours since the beginning of training in a motor learning task [48]. Importantly for our discussion, myelin changes associated with learning of a new motor skill can be detected with advanced neuroimaging in rodents[49], and also in humans as discussed below. Modern optogenetic tools allow for direct testing of the effects of neuronal activity in targeted populations of neurons on myelination. When cortical projection neurons in the motor planning area (M2 cortex) are stimulated at physiomimetic frequencies in awake, behaving mice such that a specific motor behavior is evoked, a transient proliferative response is observed in the OPC population, followed by new oligodendrocyte formation, increase in myelination within the premotor circuit, and improvement of motor performance that depends on the myelin changes [50].

Concordant with the role of adaptive myelination in motor learning, abundant new evidence suggests that neural circuit tuning through activity-regulated oligodendrogenesis and myelination is essential to a range of cognitive processes including attention, memory and multiple forms of learning. Adaptive myelination contributes to attention and short-term (<5 min) memory as measured by the Novel Object Recognition Test [12]. Furthermore, new oligodendrogenesis is central to memory consolidation as measured in fear learning (contextual fear conditioning), spatial learning (water maze), and schema-like paired associates learning (flavor-place) tasks in rodent models [51–53].

In addition to the roles for myelin plasticity in attention, memory and learning, activity and experience-regulated changes in myelin are implicated in a range of neurological and neuropsychiatric functions. An oligodendroglial response similar to that described above with selective, circuit-specific myelination is also observed with pharmacogenetic stimulation of somatosensory axons [54]. Monocular deprivation and environmental enrichment alters expression of myelin basic protein (MBP) in primary visual and somatosensory cortex, respectively [55]. Myelin remodeling in the primary visual cortex precipitated by mononuclear deprivation appears to be neuron class-specific, as it resulted in an increase in plasticity of the myelin wrapping the parvalbumin-expressing GABAergic interneurons, while the myelin around the axons of excitatory callosal projection neurons maintained its baseline level of plasticity despite the change in sensory input[56]. Social experience is yet another example of a powerful driver of myelination, particularly in prefrontal cortex; social deprivation causes prefrontal cortex hypomyelination and contributes to impaired social behavioral functioning [57,58].

Hallmark studies in humans also observed consistent, sustained and circuit-specific white matter changes in response to experience. This intriguing possibility was first suggested by cross-sectional research into the populational variation in the white matter architecture of the visuospatial attention pathways and parts of corpus callosum and its correlation with circuit-specific behaviors measured using a visual choice reaction time task and bimanual coordination task[59,60]. Furthermore, long-term motor training such as that required for learning to play a musical instrument correlated with regionally specific changes in white matter tracts [61,62] Specifically,

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professional pianists have increased white matter integrity measured by MRI DTI in the right posterior limb of the internal capsule compared to age-matched non-musicians, which correlated with number of hours of piano practice especially during childhood years. The observational studies above were followed by experimental evidence for rapid white matter changes detected on imaging within 6 weeks of learning a complex novel visuo-motor task [46]. In this study, 48 healthy adults were assigned to either learn the classic 3-ball juggling cascade, or to an untrained control group. Using diffusion tensor imaging, the research team detected significant increase in fractional anisotropy, a marker of white matter integrity, in posterior intraparietal sulcus (a region implicated in visuomotor coordination) in the training group only, that persisted for at least 4 weeks of no juggling. Such observations of how white matter dynamics are influenced by human experiences are complemented by the cognitive changes observed with white matter compromise. The visual circuit white matter deficits detected on imaging in pediatric brain tumor patients after cranial radiation predicted delayed reaction times during a visuo-motor task, and also correlated with decreased neural synchrony in the visual cortex[63] (also an excellent review of white matter dysfunction in context of human cognitive impairment here [64]).

Several mechanistic models have been proposed to underpin adaptive myelination at the cellular and/or molecular scale. Early pioneering investigations suggested that OPCs proliferate in response to electrical activity of neighboring axons through the paracrine release of growth[65,66]. More elaborate later models include a number of paracrine signaling molecules such as BDNF[12,67], neuregulin [57,67], and endothelin[68]. Both BDNF and neuregulin are proposed to work as a switch from activity-independent to activity-dependent myelination[67]. Both neuregulin[57] and endothelin[68] are depleted in rodents socially isolated during a critical developmental window, which is associated with myelination deficit. Finally, BDNF-TrkB signaling - further discussed in later section of this review - was shown to be required for adaptive myelination of cortical projection neurons[12]. Some of this molecular machinery is known to be impacted by various chemotherapy regimens[69–71], and in some cases has already been established as a mediator of chemotherapy-induced cognitive impairment in rodent models[12]. As discussed in detail below, loss of myelin plasticity after chemotherapy appears to contribute importantly to chemotherapy-related cognitive impairment.

III. Myelin dysregulation following chemotherapy

1. Evidence from patient studies. Clinical observations regarding the deleterious effects of chemotherapy on white matter integrity and myelination demand a deeper mechanistic understanding. Most studies to date report white matter changes after chemotherapy detected by use of routine imaging modalities, which allow for limited insight into the nature of white matter changes. Thus, their exact etiology, and the specific role of myelin homeostasis and plasticity is difficult to infer. This section will hence focus on the available clinical evidence for white matter changes in patients treated with chemotherapy, but the studies that include measures correlating with aspects of myelin biology will be further highlighted. Wider application of newer techniques that can elucidate aspects of brain microstructure (reviewed here [72]) might expand our understanding of white matter impairments in patients after chemotherapy and complement the conclusions drawn from pre-clinical studies of this phenomenon. Furthermore, because including a control cohort of cancer patients that are not treated with chemotherapy is not always feasible in clinical studies, untangling the effects of chemotherapy from the effects of ongoing malignancy can be difficult as well.

The magnitude of the effect of chemotherapy on cognition and the white matter tracts impacted vary across the different patient cohorts (age, type of neoplasm, treatment regimen; comprehensive summary in Table 1). Frontal white matter appears to be most commonly affected by chemotherapy [13,17,6,73], particularly in younger patients treated for hematological malignancies. The neurocognitive deficits commonly reported post-chemotherapy also localize neuroanatomically, at least in part, to the frontal white matter tracts. These observations are in line with the timeline of developmental myelination discussed above [27,28], and point to chemotherapy-induced myelination impairment over overt myelin injury, although conclusively confirming such hypothesis requires longitudinal imaging data that is currently lacking.

In addition to the reports from pediatric acute lymphoblastic leukemia survivors discussed above, much clinical evidence comes from reports of breast cancer survivors [17,74,7,75,18,16,76], tested at up to a decade post-treatment [77,78], and reports of cognitive impairment in patients treated for other cancers continue to emerge as well ([79,14,80,81], find Table 1 for a summary). The type of chemotherapy regimen is another variable driving the diversity of patient responses. For example, subtle to no effect of chemotherapy was reported in cohort of breast cancer patients undergoing an anthracycline-based treatment [75] in contrast to the otherwise methodologically similar study by Deprez et al. where 5-fluorouracil was included in the regimen [7].

Another challenge in assessing the impact of chemotherapy on white matter integrity is added by its age- and time-dependent variability. Younger premenopausal breast cancer patients treated with 5-FU-based regimen experienced neurocognitive decline that correlated with white matter changes at 3-5 months post-treatment [7,74]. However, both the white matter changes and the cognitive symptoms reversed themselves when the same cohort was reevaluated 3-4 years after treatments[15]. On the other end of the age spectrum, after methotrexate administration for childhood ALL, patients with MRI-detectable white matter changes were significantly younger than those with normal MRI findings [13], suggesting that very young age might render higher susceptibility. Furthermore, use of different timepoints for post-treatment evaluation – from immediately after chemotherapy[13] to >10 years after chemotherapy[14,78] – makes comparisons between studies less reliable both due to possible white matter recovery[15] and the effect of normal aging on white matter microstructure[82]. Overall, it appears a larger prospective longitudinal imaging study in patients after chemotherapy is warranted to outline the temporal course of myelin changes after chemotherapy. Both the particular sensitivity of frontal white matter in younger patients [13,17,6,73], and the prolonged nature of both cognitive impairment and abnormal imaging findings [14,78], as well as pre-clinical insights into dynamics of oligodendroglial lineage cells [4] hint at a protracted and ongoing dysfunction of homeostatic myelination. This is in contrast to cranial radiation-induced white matter toxicity, where overt myelin loss is attributed a significant role [83,84]. A study tracking white matter changes from baseline to immediately after administration of chemotherapeutic agent, and throughout the recovery period would conclusively differentiate the roles of acute and prolonged white matter toxicity.

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The methods used to track white matter changes in the clinical settings is another pivotal variable in this discussion. Although earlier studies relied on standard magnetic resonance imaging (MRI) for assessment of white matter integrity after chemotherapy[13,5], the different measures collected via more advanced MRI techniques such as diffusion tensor imaging (DTI) – fractional anisotropy (FA) and mean/radial/axial diffusivity (MD, RD, AD) – can provide further insights. In brief, FA is a measure of degree of diffusion within the axis of the white matter track, while MD is a measure of magnitude of diffusion in all directions[85]. Decrease in FA and/or increase in MD suggest that diffusion of the water molecules is less organized along the white matter tracks. AD is a putative axonal marker [86] that decreases with axonal degeneration, while RD is thought to increase with de- or dysmyelination [86,87]. A more in-depth and updated review of use of DTI in myelin biology can be found here [88]. Among the studies discussed so far, several report increased RD in patients after chemotherapy [73,76,77,89–91], specifically after methotrexate, 5-flourouracil, taxane and/or platins-based regimes in patients with ALL or breast cancer. Although an improvement over standard MRI in terms of discerning the role of abnormal myelin in chemotherapy-mediated white matter abnormalities, DTI is still fairly non-specific, especially compared to the newer imaging modalities that have yet to be used for patients with chemotherapy-induced cognitive impairment[72]. Overall, the field of cancer neuroscience would benefit from standardizing the methods for detecting and characterizing white matter changes after chemotherapy as well as incorporating newer imaging techniques that allow differentiating between the elements of white matter microstructure (e.g. myelin vs axons).

Aside from the ample evidence of white matter disease detected on imaging in patients after chemotherapy, other clinical data are available that suggest pathological processes specifically to the myelin component of white matter. Since the levels of myelin basic protein (MBP) in CSF can be used as a biomarker of demyelination process[92], studies have used it to assess myelin changes during and post-chemotherapy[8,93]. Moreover, depletion of oligodendrocyte lineage cells is evident in the frontal subcortical white matter in post-mortem tissue samples of patients treated with multiagent chemotherapy; such oligodendroglial depletion was not evident in the gray matter of the same subjects[11].

Much of the evidence derived from patient studies on the impact of chemotherapy on myelin health have already been recapitulated in pre-clinical models, allowing to begin investigating its mechanistic underpinnings. Specifically studies of animal models report neurocognitive deficits [11,12,93], changes in OL lineage [9,12,11,93] and decreased fractional anisotropy in corpus callosum and other white matter tracks [93] after treatments with chemotherapeutic regimens.

2. Microenvironmental factors.

In a juvenile mouse model of high-dose methotrexate (MTX)-induced cognitive impairment, oligodendroglial lineage cells are lost preferentially in the white matter and deep cortical grey matter. This decrease is driven by a loss of OPCs and mature oligodendrocytes, with a concomitant increase in late OPCs/pre-oligodendrocytes, indicating abnormal oligodendroglial lineage progression [11]. These changes were not attributed to ongoing cell death but indicated decreased OPC proliferation and increased yet incomplete OPC differentiation that persisted for up to 6 months following the MTX exposure and led to lasting deficits in myelin ultrastructure

assessed by electron microscopy. Concordantly, in a different rat model of cognitive impairment after high-dose MTX, Berlin et al. detected, in addition to the loss of oligodendroglial lineage cells in corpus callosum (CC), several correlate markers of reduced myelination – lower myelin basic protein expression by immunofluorescence, lower CC volume, and lower fractional anisotropy on DTI in several white matter tracts – up to 16 months post-treatment[93]. In a third study, MTX, 5FU and cyclophosphamide administered to rats induced myelin deficits evident at the ultrastructural and cellular levels[10]. Of note, persistent oligodendroglial lineage dysfunction was found to be due in large part to MTX-induced changes in the brain microenvironment; healthy OPCs transplanted to the environment of the previously MTX-treated brain exhibit similar dysregulation of oligodendroglial lineage progression, underscoring the central role of microenvironmental perturbation in myelin dysregulation after chemotherapy[11]

Neuroinflammation after chemotherapy.

Mounting evidence implicated cancer therapy-induced microglial/myeloid cell inflammation in mechanisms that underpin cognitive impairment (for review, please see[94]). Many forms of chemotherapy cause microglial/myeloid cell activation in the hippocampus [95,96]. In the mouse model of high-dose MTX-induced cognitive impairment, white matter microglial activation was directly induced by methotrexate[11]. This microglial reactivity in turn induces neurotoxic astrocyte reactivity (discussed in detail below), which together appear to be central to the pathophysiology of oligodendroglial lineage dysregulation and dysmyelination after high-dose methotrexate exposure. Depleting microglia/myeloid cells using a CSF1R inhibitor after MTX exposure normalizes astrocyte reactivity, oligodendroglial lineage dynamics, myelin ultrastructure and rescues cognition in high-dose MTX-treated mice[11].

Concordantly, in a rat model of cognitive impairment after the MTX, 5FU and cyclophosphamide chemotherapy regimen, an inflammatory response in the CNS was evident by increased in levels of inflammatory mediators IL-1b, TNF-a, and COX-2, and decrease of the anti-inflammatory cytokine IL-10 in the corpus callosum, also accompanied by myelin dysfunction which could be mitigated by administration of cyclooxygenase 2 inhibitor NS-393 [10].

Astrocyte reactivity is a common feature in neurological disease, and various states of reactivity can confer very different effects on disease pathophysiology (reviewed in [97]). Neurotoxic astrocyte reactivity can disrupt myelin repair in demyelinating states [98], including direct toxicity to oligodendrocytes specifically when prompted by activated microglia[99]. On the other hand, in an alternate state, neurotrophic reactive astrocytes can promote oligodendrocyte survival and maturation[100,101] and recruit immune cells to clear the lesion and allow remyelination[102]. Following high-dose MTX, broad astrocyte reactivity was observed in vivo and when astrocytes were treated with conditioned medium from MTX-activated microglia. As above, this was normalized to a large extent following microglial depletion using an CSF1R inhibitor therapy[11]

Loss of myelin plasticity. As discussed above, neuronal activity drives circuit-specific OPC proliferation, oligodendrogenesis and myelination that tune circuit function[50], and such adaptive myelination appears to be lost after MTX chemotherapy. Animals previously treated with MTX exhibit no increase in OPC proliferation, oligodendrogenesis or myelination in response to optogenetic stimulation of neuronal activity [12]. Activity-regulated brain derived neurotrophic factor (BDNF) signaling to its receptor TrkB on OPCs was found to be required for activity-regulated myelination of cortical projection neurons, and neuronal BDNF expression is lost after

MTX chemotherapy [12]. Microglial depletion with CSF1R inhibitory therapy restores neuronal BDNF expression and rescues myelin plasticity [12].

Among the available chemotherapy regimens, MTX is one of the most neurotoxic. It is not yet known if disruption of adaptive myelination is an MTX-unique or if other chemotherapy agents share a similar mechanism. A number of additional mechanisms contributing to adaptive myelination have already been described, including those relying on vascular endothelin [68] or neuregulin[67] signaling. Certain chemotherapy agents are known to deplete these signals[69–71], but their role in post-treatment myelin dysfunction is yet to be explored. Nonetheless, in a recent study, myelin decompaction in a post-platinum chemotherapy animal model of chemotherapy-related cognitive impairment was normalized with administration of retinoid X receptor agonist, a treatment that also led to activation of neuregulin pathway[103].

3. Role of myelin-intrinsic mechanisms in myelin aplasticity. Although the context of the pathological process (such as the brain microenvironment of a cancer patient treated with a chemotherapy regimen) is often just as critical for its understanding as the process itself, we will begin the discussion of the known and potential mechanisms of chemotherapy-induced myelin toxicity with those primarily relying on cell-intrinsic disruption of myelin biology.

Direct oligodendrocyte lineage toxicity. A first point to consider is the direct effect of chemotherapeutic on oligodendrocyte lineage cells. The loss of OPCs after chemotherapy has been observed in both patients[11] and animal models of chemotherapy-induced cognitive impairment[9,11,93]. *In-vitro*, clinically relevant concentrations of antimetabolite 5-fluorouracil (5-FU) were toxic to both OPCs and non-dividing oligodendrocytes, but not to many cancer cell lines[9], suggesting that being in a state of active cell division is not sufficient to confer cell susceptibility to 5-FU, but that it has oligodendrocyte-lineage-specific toxicity. Similar patterns were earlier shown for carmustine (BCNU), cisplatin (two DNA damaging agents), and cytosine arabinoside (Ara-C, an antimetabolite) chemotherapy regimens *in-vitro* and *in-vivo*[104]. In the Han et al. study, clonal analysis at sublethal doses of 5-FU revealed progenitor cells to be particularly vulnerable[9]. *In-vivo*, a long-lasting suppression of OPC proliferation in the corpus callosum was observed after 5-FU, accompanied by loss of myelin integrity. Similarly, the antimetabolite methotrexate (MTX) is directly toxic to OPCs[11]. However, OPCs are robustly self-regenerating in the healthy brain, so even a few remaining OPCs should repopulate the brain on discontinuation of chemotherapy. As this does not occur, it suggests a complex pathophysiology involving alterations to the microenvironment may be involved, as discussed in detail below.

Myelin metabolism. Myelin synthesis is a complex and expensive undertaking. During peak myelination, an oligodendrocyte of a rat synthesizes three times the weight of its cell body in myelin every day[105]. The availability of raw materials can become a limiting factor in the process of myelination. As an example, folic acid is necessary for synthesis of both nucleic acids and methionine, the latter being essential for myelination[106]. Methotrexate (MTX)-based chemotherapy acts by depleting folic acid. Indeed, cerebrospinal fluid of pediatric ALL patients treated with MTX showed signs of impairment of methionine metabolism and subclinical demyelination [8]. Furthermore, MTX white matter toxicity in patients treated for primary central nervous system lymphoma was predicted by polymorphisms of genes regulating methionine metabolism[20,21]. Finally, in pediatric leukemia there is some evidence that MTX neurotoxicity is exacerbated by concurrent use other medications (e.g. nitrous oxide anesthesia) that interact with the same biosynthetic pathway[107].

IV. Promising therapeutic strategies for preventing and/or reversing chemotherapy-induced myelin dysfunction.

Targeting microenvironmental factors. In view of the evidence indicating a central role for neuroinflammation in myelin dysregulation after chemotherapy, targeting neuroinflammation appears a plausible strategy. A partial rescue of myelin integrity and associated cognitive impairments was achieved in a rat model of cyclophosphamide, MTX, and 5-FU exposure using cyclooxygenase inhibitor therapy [10]. Consistent with such observations, patients with subacute development of multifocal leukoencephalopathy after chemotherapy (especially fluorouracil and levamisole but also others) improve with administration of corticosteroids[108–110].

Microglial activation appears to be central to myelin dysfunction after cancer therapies like methotrexate, and accordingly microglial depletion using colony-stimulating factor 1 receptor (CSF1R) inhibitor therapy normalizes oligodendrocyte lineage dynamics and rescues both myelination and cognitive function[11]. In MTX-induced failure of adaptive myelination, the interaction between secreted neuronal BDNF and its receptor TrkB on OPCs is disrupted [12]. Through mechanisms that have yet to be understood, microglial reactivity induces a downregulation of neuronal BDNF expression. Restoring TrkB signaling using a blood-brain-barrier-permeable TrkB partial agonist (LM22A-4) promotes myelination similarly to BDNF and rescues cognitive performance after MTX. Of note, the effect was specifically mediated via the effect of LM22A-4 on OPCs, as cognitive rescue depended on OPC-expression of TrkB. These targeted approaches may translate to improved cognitive outcomes after chemotherapy but require clinical studies for further evaluation.

As the molecular, cellular and microenvironmental mechanisms underlying cognitive impairment after chemotherapy come to light, clinical and translational scientists are further empowered to interrogate novel and existing therapeutic strategies to combat the long-term impact of cancer treatments on myelin health and plasticity. The impaired OPC differentiation observed in a murine model of juvenile high-dose MTX discussed above[11] also underlies remyelination failure associated with normal aging, which in aged rats can be tackled with alternate-day fasting or a well-tolerated oral anti-hyperglycemic medication metformin[111]. Not only did metformin, a small-molecule fasting mimetic, rescue the capacity of OPCs isolated from aged animals to respond to pro-differentiation factors in-vitro, but when administered to aged animals prior to and during the recovery from a focal demyelination injury, this drug allowed for significantly higher percentage of axons to be remyelinated [111]. These preclinical findings, as well as others suggesting that metformin may decrease neuroinflammation, promote hippocampal neurogenesis and spatial learning, expand and activate the endogenous pool of neural stem cells in health and in preclinical models of ischemia and neurodegeneration [112–115], provided the foundation for a randomized pilot clinical trial of metformin with cross-over design in survivors of pediatric brain cancers [116]. This pilot trial included 24 patients previously treated for childhood brain cancer (with various regimens of multi-agent chemotherapy and cranial radiotherapy) who were randomly assigned to complete either (AB) a 12-week cycle of metformin (A) followed by a cycle of placebo (B) or the two treatments in reverse order (BA). The patients were 8-20 years old and were enrolled 6-7 years since the original tumor diagnosis. In addition to testing drug safety and feasibility, cognitive testing and MRI measurements were performed at the endpoints. In this early-phase study, metformin was well tolerated, and most patients adhered well to the study treatment

protocols. Furthermore, a panel of cognitive tests revealed some improvements in immediate verbal recall and working memory after treatment with metformin. Evidence of benefit was further corroborated by increased myelin integrity on MRI after metformin treatment in the same study. Although this was an early phase study with a small cohort of patients previously treated with both chemo- and radiotherapy, the documented structural changes and cognitive improvements associated with metformin treatment are promising and warrants further investigation of this strategy in larger clinical studies.

The mechanism by which metformin mitigates cognitive impairments after cancer therapy is likely a multifaceted one like the pathology itself. In a similar fashion, aerobic exercise was earlier demonstrated to improve cognition and white matter integrity in another clinical study by the same research team[117]. Specifically, 12 weeks of exercise training in a group setting resulted in increase in fractional anisotropy on MRI in survivors of pediatric brain tumors who were previously treated with cranial radiation and chemotherapy, and such structural changes correlated with decrease in reaction time on a battery of neuropsychiatric tests. The results discussed here highlight that cognitive impairment associated with cancer treatments, including aplastic myelin after chemotherapy, are reversable and can be therapeutically mitigated.

Targeting myelin-intrinsic factors. While chemotherapy-induced myelin dysregulation is likely a multifaceted process involving several components of the CNS microenvironment [12,50], directly promoting myelination may still offer a clinical benefit. As loss of myelin integrity is a feature shared by multiple neurological disorders, several therapeutic strategies have been explored to address it. Drug-screening studies have identified compounds that promote myelination[118], which have been chiefly tested in the context of demyelinating diseases. In the experimental autoimmune encephalomyelitis rodent model of relapsing-remitting multiple sclerosis, anticholinergic benztropine promoted remyelination primarily by driving OPC differentiation[119]. Furthermore, benztropine has been shown to mitigate oxaliplatin-induced peripheral nerve demyelination and symptoms of peripheral neuropathy in mice [120]. In a chemotherapy-specific context, nasal administration of mesenchymal stem cells[121] or mitochondria isolated from human mesenchymal stem cells [122] reversed cisplatin-induced loss of myelin density in the cingulate cortex as measured by Black Gold II staining while also improving cognitive deficits in a mouse model, as does administration of RXR-agonist bexarotene[103].

V. Conclusions and future directions.

Dysregulation of myelin is an important component of the adverse effects of chemotherapy. As the roles for myelin plasticity in healthy cognitive function become increasingly clear, the potential roles of myelin aplasticity after cancer therapies come into focus.

Successful translational investigations into chemotherapy-mediated myelin disease rely on availability of clearly defined measures of myelin injury in patients undergoing chemotherapy. The lack of prospective longitudinal studies with a control cohort of no-chemotherapy patients with the same neoplasm as the treatment group is one challenge, as many cancer patients experience cognitive impairments even prior to receiving chemotherapy[123]. Prioritizing modern techniques for assessment of white matter integrity that provide insight into its pathophysiology

[86,87] would provide even further guidance for untangling the neurotoxicity of chemotherapy. Finally, clearly outlining the temporal course of pathological changes in the brain of patients after chemotherapy would allow to design and investigate faithful animal models to the extent of detail needed for development of targeted therapies.

From the viewpoint of the basic science inquiries into chemotherapy-related myelin dysfunction, much is yet to be uncovered. Although based on the evidence from patient studies, many chemotherapy regimens appear to lead to abnormal myelin dynamics, but the mechanistic underpinnings of such phenomenon were only sorted out for a selected few (such as MTX[12,12] and 5-FU[9]). To what extent these mechanisms, and the potential treatments designed based on them, will extend to other agents is yet unclear. On the other hand, emerging evidence suggests that at least some of these pathophysiological mechanisms underlying CRCI may be shared in other syndromes of "brain fog" such as long COVID-related cognitive dysfunction ([124]).

As progress in understanding neurobiology of cancer therapy-related cognitive impairment advances, new treatment strategies will manifest. Our understanding of neural plasticity, and the interaction of chemotherapeutic agents with the dynamic cellular populations of the nervous system, are paving the path for meaningful improvements to the quality of life of cancer survivors.

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Table 1. Summary of clinical reports of myelin dysfunction following chemotherapy

Neoplasm (core CT regimen)	Age of the cohort	Design; control cohort(s)	Time of the last assessment	Technique used; WM findings	Anatomic distribution of the WM findings	Functional impairments; associations with WM findings	Ref
ALL (MTX)	Mean 4.1y	Retrospective; healthy siblings	Mean 6 years since diagnosis	MRI; lower WM volumes	Only global findings reported	Attention, intelligence, and academic performance; correlated with WM findings	[5]
ALL or Non-Hodgkins Lymphoma (MTX)	Median 5.3y	Prospective; pre-CT assessment	Within 7mo of pre-treatment assessment	DTI; reduced FA and increased ADC	Frontal WM	Not tested	[6]
Breast (FEC+/-T)	Mean 45.4, premen opausal	Prospective; pre-CT assessment, age matched	3-5mo post-CT	DTI; reduced FA	Widespread regional changes	Attention, psychomotor speed, and memory;	[7]

		healthy controls, no-CT group,				correlated with WM changes	
ALL or Non-Hodgkins Lymphoma (MTX)	Range 0.7y to 8.7y	Randomized clinical trial; age-matched reference population	At the end of treatment	CSF MBP concentration; increased CSF MBP	N/A	Not tested	[8]
Various neoplasms (various agents)	Range 6mo to 26y	Retrospective; age-matched no-CT group	Post-mortem	Olig2 staining; depletion of OL lineage cells	Frontal subcortical WM	Not tested	[11]
ALL (MTX)	Median 6.2y	Prospective; pre-CT assessment	At the end of treatment	MRI; Transient high-intensity WM changes in 9% of patients; more commonly found in younger patients	Frontal lobes	Attention; correlated with WM findings	[13]
Testicular cancer (BEP)	Mean 43.1y	Retrospective; no-CT group	Mean 14y post-treatment	MRI; increased radial kurtosis	Widespread regional changes	Cognition, memory; not correlated with WM findings	[14]
Breast (TC or TP or EC>T)	Mean 43.29y	Prospective; Pre-CT assessment, no-CT group	6mo since pre-treatment assessment	DTI, MRS; reduced FA, changes in metabolite levels	Bilateral posterior CG	Cognition, quality of life, verbal learning; some correlated with WM findings	[16]
Breast (AC +/-T)	Median 49.8y	Retrospective; age-, education-, and IQ-matched healthy controls	22mo post-CT	DTI; reduced FA	Genu of CC	Processing speed, correlated with WM findings	[17]
Breast (FEC+/-T)	Mean 43.4y for younger; mean 63.8y	Prospective; pre-CT assessment, age matched healthy	5-6mo post-treatment	MRI; WM volume expansion in the younger group only	Widespread changes	Attention / concentration, memory, and processing speed; correlated with	[18]

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	for older group;	controls, no-CT group				some WM findings	
ALL (high dose MTX + leuvocorin)	Median 14.4y	Pro- and retrospective; pre-CT assessment; population norms	Mean 7.2y since diagnosis	DTI; reduced FA, increased AD and RD (in patients with h/o acute leukoencepha-lopathy comp. to patients without)	Frontal WM	Working memory, organization, initiation, and planning; correlated with some WM findings	[73]
Breast (FEC+/-T)	Mean 45.4; premenopausal	Retrospective; matched healthy controls, no-CT group	Mean 129 days post-CT	DTI; reduced FA, increased MD	Frontal and temporal WM	Attention, processing speed, psychomotor speed; correlated with some WM findings	[74]
Breast (AC+/-T)	Mean 49.1	Prospective; pre-CT assessment, age matched healthy controls, no-CT group,	6mo post-treatment	DTI; reduced FA, increased MD (both only detected via ROI analysis)	Right SLF, right CST	Not tested	[75]
Breast (TC or TP or TH or TCPH or ddAC>T or TAC)	Over 60y	Prospective; pre-CT assessment, age- and sex-matched healthy controls	Within 1mo post-treatment	DTI; increased MD and RD	Genu of CC	None	[76]
Breast (FEC>CTC)	Mean 56.5y	Retrospective; no-CT group	At least 9 years since CT	DTI, MRS; reduced FA, increased MD and RD; changes in metabolite levels suggestive	Widespread regional changes	Verbal fluency and executive functions; no significant correlations with WM findings	[77]

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				of axonal injury			
Breast (FEC +/- CTC)	Mean 56.3 (high dose CT group), 59.8 (conventional dose CT group)	Retrospective; healthy controls, conventional dose CT group, RT only group	Average 11.5 years since CT	DTI, increased MD in high dose CT group	Widespread regional changes; mainly frontal WM	Verbal memory (lower in high compared to conventional dose CT group); associations with some WM findings	[78]
ALL (MTX) or medulloblast-oma (LCV + cranial RT)	Mean 14y	Retrospective; age-matched healthy controls	At least 3 years since end of treatment	DTI; reduced FA	Mainly frontal WM	processing and motor speed; correlated with selected WM findings	[79]
NF1-associated optic pathway glioma (vincristine + carboplatin)	Mean 7.6y	Retrospective; no-CT group	Ranging from while on treatment to 4.2y off treatment	DTI; reduced FA	CC, cerebellothalamic tracts	Not tested	[80]
Bone and soft tissue sarcoma (various agents)	Mean 12.97y	Retrospective; age- and gender-matched healthy controls	Mean 9.92y since diagnosis	Diffusion-MRI; reduced FA (widespread), lower AFD (cingulum and CC only)	Mainly centrally located WM	Selected intelligence subscores, correlated with some WM findings	[81]
ALL (various agents)	Mean 40.71y	Retrospective; age-matched controls	At least 3 years since end of treatment	DTI; reduced FA and AD, increased MD and RD	Widespread regional changes	Not tested	[89]
ALL (MTX)	Mean 11.34y	Retrospective; age, sex, handedness, and socioeconomic status nearest-neighbor matched healthy controls	3–4 months post-treatment	DTI; reduced FA, increased RD	Widespread regional changes	Lower processing capacity, not correlated with WM findings	[90]

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ALL	Range 8-18y	Retrospective; healthy controls	Mean 8y since diagnosis	MRI; reduced WM and GM volume, decreased FA, increased RD	Widespread, with exception of occipital lobe	Full-scale IQ	[91]
Various neoplasms (various agents)	Range 6mo to 26y	Retrospective; age-matched no-CT group	Post-mortem	Olig2 staining; depletion of OL lineage cells	Frontal subcortical WM	Not tested	[11]

Table abbreviations: CT = chemotherapy; WM = white matter; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; AD = axial diffusivity; ADC = apparent diffusion coefficient; AFD = apparent fiber density; MRS = magnetic resonance spectroscopy; CC = corpus callosum; CG = cingulate gyrus; SLF = superior longitudinal fasciculus; CST = corticospinal tract; ALL = acute lymphoblastic leukemia; MTX = methotrexate; LCV = lomustine, cisplatin, vincristine; AC = doxorubicin, cyclophosphamide; T = taxanes; TC = docetaxel, cyclophosphamide; TP = paclitaxel, carboplatin; EC = epirubicin, cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; CTC = cyclophosphamide, thiotepa, carboplatin; TH = docetaxel, trastuzumab; TCPH = docetaxel, carboplatin, trastuzumab; ddAC = dose dense doxorubicin and cyclophosphamide; TAC = docetaxel, doxorubicin, and cyclophosphamide; BEP = bleomycin, etoposide, cisplatin; RT = radiotherapy; h/o = history of

Figure 1: Myelin plasticity and Aplasticity. (left) Neuronal activity regulates oligodendrocyte precursor cell (OPC, yellow) proliferation, the generation of new oligodendrocytes (yellow) and the addition of new myelin internodes (yellow), or remodeling of existing myelin internodes. These activity-regulated changes in myelin are thought to tune neural circuit function and contribute to healthy cognition. (right) Some cancer chemotherapies such as methotrexate cause microglial reactivity (red) and consequent dysregulation of neuron-oligodendroglial interactions, resulting in loss of myelin plasticity. Created with BioRender.com.

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Highlights:

- Myelination is a dynamic process throughout lifetime and this plasticity of myelin contributes to cognitive function
- Multiple methodologies detect myelin dysfunction in patients after chemotherapy, with possible neuroanatomical and age-dependent patterns
- Both cell-intrinsic biology and microenvironmental interactions of myelin-forming cells are dysregulated after chemotherapy
- Several therapeutic strategies have been explored in preclinical studies to overcome myelin dysregulation post-chemotherapy

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