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Review

Prevention of anticancer therapy-induced neurotoxicity: Putting DNA damage in perspective

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a severe side effect of conventional anticancer therapeutics (cAT) that significantly impacts the quality of life of tumor patients. The molecular mechanisms of CIPN are incompletely understood and there are no effective preventive or therapeutic measures available to date. Here, we present a brief overview of the current knowledge about mechanisms underlying CIPN and discuss DNA damage-related stress responses as feasible targets for the prevention of CIPN. In addition, we discuss that the nematode *Caenorhabditis elegans* is a useful 3R-conform model organism to further elucidate molecular mechanisms of CIPN and to identify novel lead compounds protecting from cAT-triggered neuropathy.

1. Introduction

The efficacy of anticancer therapeutics is limited by agent-specific adverse effects. Apart from impacting prognosis, acute or persisting therapy-induced normal tissue damage substantially impacts the patient's quality of life. Early-onset of therapeutic actions aiming to lower distressing adverse effects significantly prolong the patient's five-year survival rates (Temel et al., 2010). This highlights the fact that an optimized supportive management of adverse reactions not only improves the patient's quality of life but also the prognosis. Apart from incriminating acute and transient side effects occurring at an early time point after the onset of the therapy, delayed and irreversible therapy-induced toxicity is particularly detrimental. In consequence, next to acute life-threatening complications that may develop, continuous suffering of the patients from sustained adverse responses is a further serious problem of anticancer therapy that compromises the patient's compliance. In this context, anticancer drug-induced peripheral and central neurotoxicity is particularly noticeable (Cavaletti and Marmiroli, 2015; Cavaletti and Tredici, 1995; Chiorazzi et al., 2015; Salat, 2020b; Velasco and Bruna, 2010). Here, chemotherapy-induced (acute or chronic) peripheral neurotoxicity (CIPN) can compromise both sensory and motor functions (Velasco and Bruna, 2010). In addition, cognitive impairment may arise from anticancer therapy, too. Unfortunately, effective pharmacological measures to prevent and/or treat such stressful adverse effects are largely missing. Here, we will focus on the discussion of DNA damage-related factors as putative cellular targets for the development of neuroprotective pharmacological concepts, suggest novel compounds that might be promising to enter pre-clinical in vivo studies and/or even clinical trials, and, furthermore, discuss the nematode *Caenorhabditis elegans* as quite favorable 3R-conform in vivo model for meaningful pre-clinical research in neurotoxicology and drug development.

2. Classes of neurotoxic anticancer therapeutics and molecular mechanisms

2.1. Anticancer therapeutics evoking neuropathy

Chemotherapy-induced neuropathy can cause both central and peripheral symptoms. Central symptoms comprise cognitive deficits as well as depression and anxiety. Cognitive impairment, often referred to as chemo-brain, is of utmost clinical relevance in the context of radiochemotherapy of childhood malignancies (Mounier et al., 2020). Yet, chemo-brain has been reported in adults, too. For instance, about two-thirds of the studies dealing with chemotherapy-related cognitive dysfunction reported cognitive impairment going along with the treatment of breast cancer (Wefel and Schagen, 2012). The incidence appears to depend on the dose applied, the administration method as well as the drug combinations used. Of note, high-risk combinations have not yet been specified. Cognitive impairments were also observed in animal

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models, e.g. after treatment with CisPt (Hinduja et al., 2015; Zhou et al., 2016) or methotrexate (Seigers et al., 2009). The pathophysiology is highly complex with blood-brain barrier disruption, impaired hippocampal neurogenesis, neuroinflammation, and oxidative stress being involved (Mounier et al., 2020). Apart from cognitive deficits, central nervous system (CNS) toxicity evoked by chemotherapeutics includes acute and chronic encephalopathy, seizures, headache, cerebrovascular complications and visual loss (Newton, 2012). CNS toxicity is mainly associated with the administration of methotrexate, vincristine, ifosfamide, fludarabine, cytarabine, 5-fluorouracil, cisplatin and interferons (Sioka and Kyritsis, 2009). By contrast, it is rare for taxanes, likely because these drugs poorly pass the blood-brain barrier. Nevertheless, acute encephalopathy was occasionally reported after paclitaxel infusion, too (Ziske et al., 2002). Toxic effects of chemotherapeutic drugs on the peripheral nervous system (PNS) include chemotherapy-induced peripheral neuropathy (CIPN), which is characterized by tactile and thermal allodynia, thermal hyperalgesia, spontaneous pain, paresthesia and numbness (Cavaletti and Marmiroli, 2015; Miltenburg and Boogerd, 2014; Salat, 2020a, 2020b; Wolf et al., 2012). It is mainly caused by conventional anticancer therapeutics (cAT) such as platinating agents, vinca alkaloids, taxanes, alkylating agents, and antimetabolites as well as by individual biologicals such as immune checkpoint targeting monoclonal antibodies. Although it is mostly sensory neuropathy that is evoked by these agents, more detrimental motor neuropathy can also develop. Drug-induced toxicity occurs in an agent-specific manner, depends on the cumulative dose, evolves either acute or delayed and can be reversible or irreversible (Salat, 2020b). The incidence is agent-specific and ranges from 10% up to > 95%. The remarkable agent-specificities are highlighted for example by the tremendous variations in the incidence observed among the group of chemically closely related platinating agents. Here, the incidence of CIPN reported for carboplatin is 10–20%, for cisplatin (CisPt) 30–40%, and for oxaliplatin 60–90%. Of note, whereas neuropathy caused by CisPt or carboplatin is mostly irreversible, the acute neurotoxicity caused by oxaliplatin is usually reversible. For sake of completeness, it should be mentioned that CIPN resulting from paclitaxel or vinca alkaloids is also reversible in most patients (Salat, 2020b).

2.2. Molecular mechanisms involved in anticancer therapy-triggered neurotoxicity

Having in mind the wide range of anticancer drugs that are causing toxicity by different molecular mechanisms and their largely varying potency to evoke neuropathy, it is obvious that the pathophysiology of anticancer drug-induced CIPN is fairly complex. Among others, oxidative stress, impaired mitochondrial function and neuronal cell death have been suggested to contribute to CIPN evoked by cisplatin, carboplatin, oxaliplatin, vincristine, and paclitaxel. In addition, these cAT also disturb calcium homeostasis, promote axon degeneration by favoring myelin loss, affect neuronal excitability by causing dysfunction of various ion channels including sodium, potassium, calcium and TRP channels, and, moreover, trigger neuroinflammation as well as an activation of the immune system (Cavaletti and Marmiroli, 2015; Li et al., 2020; Salat, 2020b; Sittl et al., 2010; Starobova and Vetter, 2017). The exact molecular mechanisms involved vary in a strikingly agent-specific manner. For instance, even the chemically closely related platinating drugs cisplatin and oxaliplatin are showing striking differences regarding the molecular mechanism(s) contributing to CIPN. Here, interference with neurotransmitter signaling is more relevant for oxaliplatin, which is likely related to the metabolic formation of oxalate, a well-known calcium chelator. Hence, neurotoxicity evoked by oxaliplatin is thought to be majorly related to disturbed Ca^{2+}-signaling (Marmiroli et al., 2015; Salat, 2020a). Moreover, oxaliplatin affects neuronal excitability as regulated by voltage-gated sodium, potassium and calcium channels (Kagiava et al., 2008; Salat, 2020b; Sittl et al., 2010). CisPt also modulates the function and expression of voltage-gated calcium channels, yet has a lower preference for potassium channels than oxaliplatin (Leo et al., 2017; Salat, 2020b; Tomaszewski and Busselberg, 2007). Detailed mechanistic knowledge regarding the manifold mechanisms involved in cAT-mediated CIPN is a prerequisite for a rationality-based development of novel treatment strategies (Ma et al., 2018a, 2018b; Sisignano et al., 2014). Fig. 1 illustrates key mechanisms contributing to CIPN evoked by cAT (i.e. platinating agents and spindle poisons) (Fig. 1), putting damage to nuclear DNA, mitochondria and microtubules into focus, taking into account that these cellular structures are considered as major cellular targets for the respective classes of cAT.

Discussing the putative molecular mechanisms of cAT-triggered neurotoxicity in more detail, it is important to keep in mind that the anticancer efficacy of cAT is mainly due to a perturbation of the DNA replication of rapidly dividing malignant cells. However, since terminally differentiated neuronal cells do not proliferate anymore, it is tempting to speculate that the molecular mechanisms contributing to the adverse effects of cAT on non-proliferating non-malignant cells are substantially different from their cytotoxic effects on proliferating tumor cells. This brings up the question as to which cellular structure(s) or function(s) of neuronal cells might be preferentially targeted by platinating agents or spindle poisons to mediate the aforementioned neuronal dysfunctions. Regarding platinating agents, genomic or mitochondrial DNA appear to be a rational candidate target, having in mind that these drugs form different types of DNA adducts (i.e. DNA monoadducts and DNA intra- and interstrand crosslinks). Both the nucleus and the mitochondria harbor DNA and, moreover, nuclear DNA damage leading to transcriptional stress responses also occurs in non-proliferating cells (Ljungman, 2007; Ljungman and Lane, 2004; Ziegler et al., 2020). Of note, cisplatin-mediated neurotoxicity and ototoxicity have been related to DNA adduct formation in dorsal root ganglion (DRG) neurons and strial marginal cells of the cochlea, respectively (Cavaletti and Tredici, 1995; Meijer et al., 1999; Ta et al., 2006; Thomas et al., 2006), supporting the hypothesis that DNA damage is a major trigger of CisPt-driven normal tissue toxicity. In addition, nuclear DNA damage affects mitochondrial functions as well (Scarpulla, 2012). Vice versa, mitochondrial DNA damage and resulting mitochondrial dysfunction interferes with nuclear functions (Roos et al., 2016; Scarpulla, 2008, 2012). Notably in this context, strand breaks in mitochondrial DNA do not only disturb mitochondrial functions but, in addition, communicate with the nucleus aiming to maintain cellular homeostasis. This was concluded from the observation that mtDNA damage and nuclear DNA damage synergize to trigger a type-I interferon response (Tigano et al., 2021). The tight interplay between DNA damage-related stress responses and mitochondrial homeostasis is also illustrated by the facts that DNA damage acts as a trigger of mitophagy involving Spata18 (Dan et al., 2020) and, furthermore, the DDR-related kinase ATR plays a direct antiapoptotic role at mitochondria involving the BH3 domain of Bcl-2 family members (Hilton et al., 2015). Overall, DNA damage-related disturbance of nuclear/mitochondrial communication by platinating cAT is hypothesized to account for the overlapping neurotoxic effects triggered by this class of anticancer drugs. Detailed knowledge about such – and other - intracellular communication pathways is required for a better understanding of the complex molecular basis of anticancer drug-induced neuropathy, which in turn is mandatory for the development of reasonable neuroprotective concepts.

2.3. Possible therapeutic targets for the prevention of drug-induced neuropathy

Unfortunately, neither effective treatment of anticancer drug-induced neuropathy nor effective preventive strategies are available so far (Salat, 2020a). Several drugs have been tested in the clinic in order to cope with therapy-induced neuropathy, including for instance pregabalin, gabapentin, amifostine or glutathione, but their clinical efficacy is questionable (Beijers et al., 2012). Currently, it is the selective

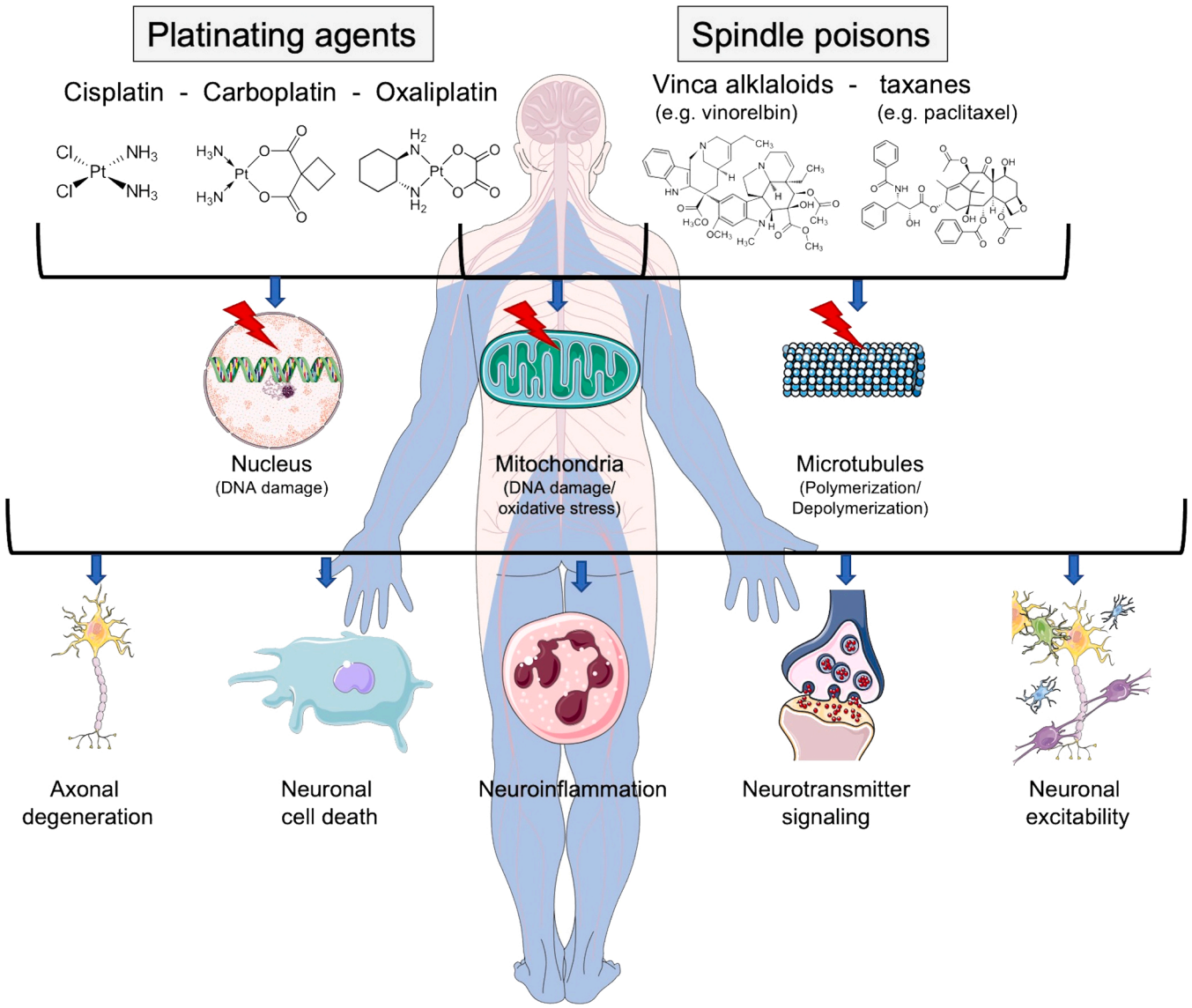

Fig. 1. Mechanisms putatively contributing to cAT-induced peripheral neuropathy (graphics: https://smart.servier.com).

serotonin noradrenaline reuptake inhibitor (SSNRI) duloxetine, which is recommended in the relevant guidelines for the treatment of CIPN (level B recommendation) (Grisold and Grisold, 2017; Jordan et al., 2020; Loprinzi et al., 2020). Examples of drug candidates that are currently in clinical studies to evaluate their potency to prevent oxaliplatin- and paclitaxel-induced CIPN are the mitochondrial manganese superoxide dismutase (SOD) mimetic calmangafodipir, the tyrosine kinase inhibitors dasatinib and nilotinib and the antidiabetic drug metformin (Glimelius et al., 2018; Salat, 2020a). Moreover, chemokine receptor antagonists are also under discussion to have beneficial effects on CIPN and associated neuropathic pain (Zhou et al., 2020). Nevertheless, there is a clear clinical need for novel pharmaco-therapeutic and -preventive options to deal with anticancer therapy-induced neuropathy.

Having in mind the manifold cellular targets and molecular mechanisms that are involved in the pathophysiology of drug-induced neuropathy (see above), there are numerous potential and reasonable targets for pharmacological intervention (Salat, 2020a). Nevertheless, deciding on a putative target that is anticipated to be particularly useful for the prevention of drug-induced neuropathy is challenging. For decision-making, it would be very helpful to know the primary (upstream) cellular target of an anticancer drug that gets majorly damaged in the very beginning and, consecutively, ultimately triggers complex molecular mechanisms that harm different types of neuronal cells. This is because it can be anticipated that pharmacological interference with mechanisms that account for initial (primary) damage formation and early processes of pathophysiology may be particularly effective for the purpose of appreciable neuroprotection. Of course, targeting secondary downstream mechanisms executing cytotoxicity might also have beneficial outcomes, yet presumably to a lower and more limited extent. As already mentioned before, it appears feasible that DNA damage induced by platinating agents in non-malignant neuronal cells is the ultimate driving force of neurotoxicity, as reflected for instance by axonal degeneration or neuronal cell death. However, although studies comprising DNA repair-deficient mice support the view that DNA damage contributes to the adverse effects (neurotoxicity/ototoxicity) evoked by platinating agents (Dzagnidze et al., 2007), the pathophysiological relevance of DNA damage remains unclear. Mitochondrial DNA damage might be equally relevant as nuclear DNA damage, especially because there is cross-talk between the nucleus and the mitochondria in response to genotoxic stress (Roos et al., 2016; Scarpulla, 2008, 2012) as already mentioned above. Recently, it has been shown that DNA damage can lead to the activation of the innate immune system (Ermolaeva et al., 2013; Gasser et al., 2005; Tigano et al., 2021). This key finding is suggestive of DNA damage-driven inflammatory responses to contribute to

the pathophysiology of chronic neuroinflammation and subsequent neuropathy evoked by anticancer therapeutics. Hence, inhibition of neuronal DNA damage formation and/or interference with early DNA damage triggered stress responses appears to be an attractive - but so far little noticed - strategy for the prevention of CIPN elicited by genotoxic cAT, including platinating drugs.

Spindle poisons such as vinca alkaloids and taxanes inhibit microtubule polymerization and depolymerization, respectively, during mitosis, thereby causing cell death of proliferating tumor cells. It is tempting to speculate that interference with microtubule-related mechanisms also contributes to neuropathy caused by spindle poisons. Having in mind that microtubular structures are important for the architecture of the cytoskeleton, shape of the nuclear envelope, nucleocytoplasmic transport and vesicle transport / axonal transport, it is rational to assume that disturbance of the microtubular homeostasis is meaningful for the development of neuropathy evoked by spindle poisons. Noteworthy in this context, similar to platinating agents, microtubule inhibitors can also cause mitochondrial dysfunction (Canta et al., 2015) and, moreover, CisPt is reported to inhibit microtubule formation (Tulub and Stefanov, 2001). Hence, there are some overlapping cellular structures, including the nucleus and the mitochondria, that are affected by both platinating drugs and microtubule inhibitors and, hence, might be exploited for the development of novel neuroprotective pharmacological strategies in the future.

On the other hand, in view of a medium-term translation of results from basic research into the clinic, it is not exclusively the most promising target that matters. Rather, it is also highly important to consider whether such target is easily druggable after all. In this context, the contribution of off-target effects of cAT to their overall neurotoxicity needs special attention, because it can't be ruled out that such (underappreciated) mechanisms are pathophysiologically more relevant in non-proliferating differentiated cells than in proliferating tumor cells. For instance, platinating agents are reported to cause manifold types of injury apart from genomic or mitochondrial DNA damage, including oxidative stress resulting from the depletion of the cellular GSH pool, activation of multiple stress-related kinases (e.g. JNK, p38, c-Abl) and induction of ER stress as well as autophagy (Lin et al., 2017; Mandic et al., 2003; Rabik and Dolan, 2007; Rebillard et al., 2008; Wisnovsky et al., 2013). Noteworthy in this context, different MAPK can either promote or protect DRG neurons from platin-induced apoptosis (Scuteri et al., 2009). Taken together, it can be assumed that manifold toxic effects contribute to the complex pathophysiology of acute or chronic neuronal dysfunctions driven by platinating drugs. In light of this confusing situation, the choice of a well-druggable and effective target with good prospects is highly demanding and piecewise a matter of luck.

3. Usefulness of novel compounds and off-label use of already approved drugs for neuroprotection

The identification of bioavailable and well-tolerable novel compounds that are useful for targeting purposes is not only challenging but also interminable. Therefore, testing of the neuroprotective efficacy of compounds that have already been extensively characterized for different purposes in preclinical models or off-label use of otherwise approved drugs, might be a more time-saving approach. Aiming to prevent adverse effects of anticancer therapeutics, it is however highly important to rule out the possibility that the tumor response is mitigated by these compounds as well. This is a serious and utmost relevant concern that presumably limits the clinical compliance of normal tissue protective pharmacotherapeutic strategies as based on the use of antioxidants or thiol-containing compounds such as the prodrug amifostine, which is reported to mitigate ototoxicity of CisPt-based tumor therapy in children (Fouladi et al., 2008; Gurney et al., 2014).

To overcome this justified concern, normal tissue-specific mechanisms might be exploited to selectively reinforce endogenous cytoprotective functions of non-malignant cells. However, molecular mechanisms determining the resistance of non-malignant cells to anticancer therapeutics are less well investigated as compared to tumor cell-related drug resistance/drug sensitivity factors. So, for the development of cytoprotective strategies against adverse effects of cAT, this focus needs to be expanded to normal tissues, including neuronal cells. In other words, instead of exploiting tumor cell-specific genetic or metabolic properties for individualized anticancer therapy, neuronal-specific features might be exploited to enable personalized neuropreventive measures. Eventually, with some luck, compounds might be identified that have opposite effects on tumor versus normal cells by promoting tumor cell killing while concomitantly protecting normal tissue from drug-induced damage. Such dual-active compounds are anticipated to have the best chance to enter clinically oriented in vivo studies in mice or even clinical trials in a relatively short time. When reflecting on drugs that may fulfill these ambitious dual requirements, we came up with inhibitors of mechanisms of the DNA damage response (DDR) and inhibitors of histone deacetylases (HDAC). Arguments for their supposed suitability concerning this matter are subsequently discussed.

3.1. Targeting factors of the DNA damage response (DDR) to alleviate neuropathy

In order to improve personalized approaches to fight cancer, clinical research has focused on the genetic identification of a subpopulation of malignant cells that is useful for targeting approaches. The therapeutic potential of targeting genetically homogenous and stable normal (neuronal) cells to alleviate dose-limiting side effects of anticancer therapeutics seems to be underappreciated. Aiming to mitigate the level of DNA damage - as a plausible trigger of platin-induced neuropathy - in primary neuronal cells, interference with mechanisms of cAT transport to lower the level of initial DNA damage or activation of DNA repair mechanisms to promote a rapid removal of DNA adducts are optional. However, activation of cellular functions (e.g. DNA repair) by pharmacological measures is rather difficult to realize as compared to inhibitory strategies, as implemented for instance by inhibitors of tumor-related oncogenic kinases. Thus, selective stimulation of tissue-protective factors in order to prevent neuropathy following cAT treatment appears difficult to realize. Having in mind that platinating agents are causing DNA damage, thereby activating complex mechanisms of the DDR, targeting DDR-related signaling is hypothesized as a possibility to counteract platin-induced neuropathy. Since the DDR is known to define the balance between survival and death by triggering either cell death or by promoting survival mechanisms (Harper and Elledge, 2007; Roos et al., 2016; Zhou and Elledge, 2000), the selective inhibition of pro-apoptotic DDR-related mechanisms seems to be a conceivable option to mitigate cAT-stimulated neuronal cell death. However, the neuroprotective effectiveness of such DDR-related approaches has not yet been investigated.

Nowadays, targeting DDR mechanisms is believed to be a powerful strategy to improve anticancer therapy (Fokas et al., 2014; Ljungman, 2009; Lord and Ashworth, 2012; Slade, 2020; Zhu et al., 2020). Having this in mind, we wonder whether well-established pharmacological inhibitors of DDR-related kinases (such as e.g. ATM, ATR, Chk1/2, Wee1, HIPK2) or inhibitors of p53-related detrimental functions might be useful not only for improving tumor cell kill but also for mitigating adverse neurotoxic effects of cAT. Regarding p53, which can both promote apoptosis and cell survival, it has been shown that Ser46 phosphorylation by HIPK2 switches this tumor suppressor protein towards a stimulator of cell death (Bitomsky and Hofmann, 2009; Conrad et al., 2016; Hofmann et al., 2013; Liebl et al., 2021). Hence, we speculate that inhibition of HIPK2 might be worth the effort to protect neuronal cells from cAT-triggered p53-regulated cell death. The PI3-like kinase ATM is another candidate target when aiming to protect normal tissue from cAT-induced toxicity. This hypothesis is based on the observation that a fibroblast-specific murine ATM knock-out, as well as pharmacological inhibition of ATM, mitigate cardiotoxicity induced by the anthracycline

derivative doxorubicin (Zhan et al., 2016). Moreover, targeting of the DDR is likewise useful to prevent acute kidney injury (AKI) evoked by CisPt (Yan et al., 2016). Most important in the context of this review, suppression of ATM also attenuates genotoxin-induced apoptosis of postmitotic neurons (Kruman et al., 2004). This may be related to the fact that primary neurons enter M-phase under pathological conditions (Walton et al., 2019). In this context it should be mentioned that the interplay between ATM, HDAC1, and SIRT1 maintains genomic stability of neurons under basal situation, thereby counteracting neurodegenerative disorders (Dobbin et al., 2013). Moreover, in the absence of DNA damage, ATR/Chk1 signaling is involved in axon regeneration and is considered to be neuroprotective (Roos et al., 2016; Scarpulla, 2008, 2012; Ye and Blain, 2011). Hence, forthcoming in vitro and in vivo studies systematically investigating the neuroprotective potential of selected DDR modifiers in the context of CIPN are preferable (Fig. 2).

3.2. *Targeting histone-deacetylases for the prevention of anticancer-therapy induced neurotoxicity*

Histone/protein deacetylases (HDACs) regulate manifold cellular functions, including gene expression, cell cycle progression, and tumorigenesis (Haberland et al., 2009; Hadley et al., 2019; Roos and Krumm, 2016; Seto and Yoshida, 2014; Wang et al., 2001). They are often deregulated during cancer development and can confer drug resistance by affecting mechanisms of cell death, cell cycle checkpoint regulation as well as DNA repair and DNA damage response (Bolden et al., 2006; Goder et al., 2018; Kachhap et al., 2010; Roos and Krumm, 2016). According to the requirement of Zn^{2+} or NAD^{+}, HDACs are sub-grouped into four different classes, (i.e. class I, II, and IV (Zn^{2+} dependent) and class III (NAD^{+} dependent)). Class I HDACs comprise the isoforms HDAC1, 2, 3 and 8, class IIA consists of HDAC 4, 5, 7 and 9, class IIB of HDAC6 and 10, class IV of HDAC11 and class III is represented by the sirtuins (SIRT1–7) (Seto and Yoshida, 2014; Van Dyke, 2014). Histone deacetylase inhibitors (HDACi) are approved for the therapy of leukemias and are in clinical studies for the therapy of solid tumors as well (Bian et al., 2015; Bolden et al., 2006; Eckschlager et al., 2017; Lernoux et al., 2020). Most important in the context of this review, HDACi interfere with mechanisms of DNA repair and DDR (Goder et al., 2018; Kotian et al., 2011; Miller et al., 2010; Roos and Krumm, 2016; Zhao et al., 2017) and synergistically increase the anticancer efficacy of several cAT, including CisPt, in vitro (Stenzel et al., 2017; Suraweera et al., 2018; Xie et al., 2013). Yet, it should be noted that HDACi are also under investigation for the therapy of non-malignant diseases, especially cardiovascular and neurological disorders (De Simone and Milelli, 2019; Habibian and Ferguson, 2018; Thomas and D'Mello, 2018), making it tempting to speculate that HDACi might also be useful to mitigate adverse effects of cardio- or neurotoxic cAT.

Depending on the class of HDAC that is targeted, HDACi execute both beneficial and detrimental effects on neurons (Ma and D'Mello, 2011; Thomas and D'Mello, 2018). For instance, HDAC1 and other class I/II HDACs are suggested to contribute to the neuronal p53-related protective branch of the DDR, indicating that HDACi may enhance neurotoxicity resulting from DNA damage occurring during neuronal development (Vashishta and Hetman, 2014). However, out of the different classes of HDACs, especially inhibition of HDAC6, which is a microtubule-associated cytoplasmic deacetylase (Hubbert et al., 2002), is reported to alleviate CIPN induced by vinca alkaloids in vivo (Van Helleputte et al., 2018). Moreover, inhibition of HDAC6 counteracts CisPt-induced neurocognitive impairment in male mice (Ma, et al., 2018a, 2018b). This is going along with a reversal of CisPt mediated

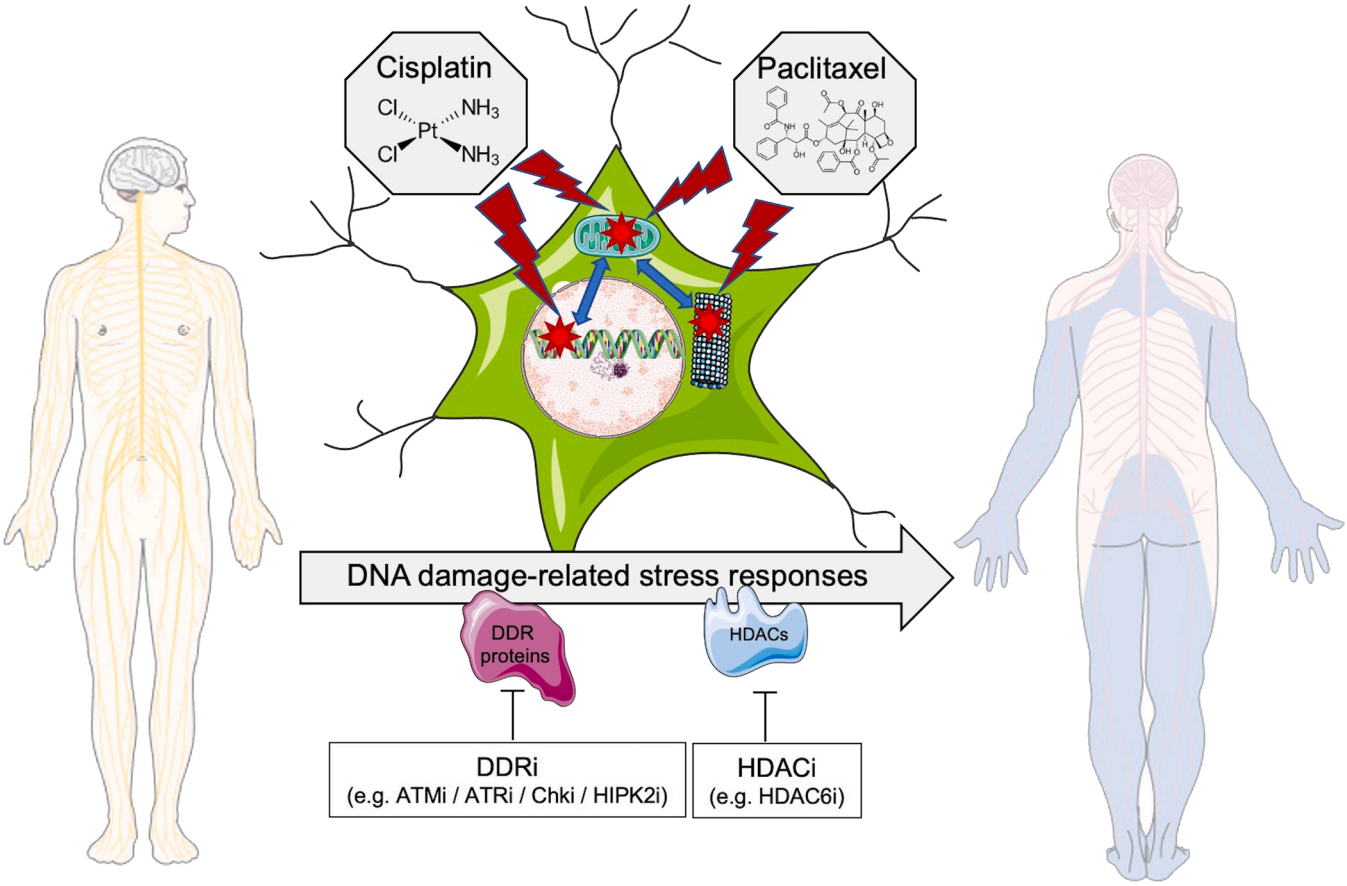

Fig. 2. Targeting of DNA damage-related stress responses by DDR inhibitors (DDRi) and HDAC inhibitors (HDACi) to alleviate cAT-induced peripheral neuropathy (graphics: https://smart.servier.com).

detrimental effects on mitochondrial activity and synaptic integrity. Of interest, CisPt causes deacetylation of the microtubule protein alpha-tubulin and hyperphosphorylation of the microtubule-associated protein tau. Again, all these deleterious platin effects were reversed by HDAC6i (Ma et al., 2018a, 2018b). Furthermore, brain permeable HDAC6i is able to improve memory and learning in a mouse model of fragile X-syndrome (Kozikowski et al., 2019). These data highlight the putative usefulness of HDAC6i in fighting chemotherapy-induced neuropathy (Fig. 2). Having in mind that HDAC6 is also a promising target to improve anticancer therapy (Auzmendi-Iriarte et al., 2020; Banik et al., 2019, 2020; Knox et al., 2019), HDAC6i seem to be a particularly useful dual-active compound to widen the therapeutic window of platin-based anticancer therapy. Besides, pan-HDACi are described to alleviate CisPt-induced nephrotoxicity (Liu et al., 2018; Tang and Zhuang, 2016), likely by stimulating protective autophagy-related mechanisms, pointing to a broader usefulness of pan-HDACi in the prevention of anticancer therapy-induced adverse effects. Similar to their application as anticancer therapeutics, it can be assumed that the selection of appropriate class- and isoform-specific HDACi is required to achieve specific and effective normal tissue-specific protection, including neuroprotection.

4. Exploiting the nematode *Caenorhabditis elegans* to illuminate the pathophysiology of CIPN and to identify and characterize the molecular mode of action of novel neuroprotective compounds

Seeking for novel and well-tolerable compounds that can alleviate anticancer therapy-induced neuropathy, for instance by interfering with mechanisms of the DDR or HDAC functions, adequate test systems enabling high throughput compound screenings are required. Because of the complex pathophysiology of drug-induced neuropathy, the usefulness of 2D- or even 3D- in vitro systems is questionable as they only poorly reflect the relevant in vivo physiology. In principle, painful peripheral neuropathy evoked by platinating drugs can be analyzed in mice (Carozzi et al., 2015; Renn et al., 2011), but large scale compound testings in order to identify novel neuroprotective lead compounds are technically difficult, time-consuming, costly and subject to ethical concerns in in vivo models of CIPN. Therefore, alternative 3R conform models might be particularly useful. Here, the nematode *C. elegans* appears to be well suitable because of its cost-effective cultivation, small size and high progeny number. Moreover, it is already well established in neurological and neurodegenerative research (Byrne and Hammarlund, 2017; Lopes et al., 2020). For instance, the nematode was exploited for pioneering research in Alzheimer's and Parkinson's disease (Griffin et al., 2017; Martinez et al., 2017) and, furthermore, is an emerging model in toxicology (Honnen, 2017; Hunt, 2017). The usefulness of *C. elegans* for the investigation of neurotoxicity is supported by the fact that the nematode has most of the human relevant neurotransmitters and related receptors (Brenner, 1974; White et al., 1986). In addition, the nematode's sensitivity to the neurotoxic effects of platinating agents, as reflected by a decrease in pharyngeal activity, is highest for CisPt (Honnen et al., 2017), which mimics the clinical situation in humans (Amptoulach and Tsavaris, 2011). Furthermore, the selective serotonin noradrenaline reuptake inhibitor (SSNRI) duloxetine, which is clinically used for the treatment of CIPN, was shown to prevent CisPt-driven neurotoxicity in *C. elegans* (Wellenberg et al., 2021a). Apart from impacting serotonergic neurotransmission (as reflected by the reduction of pharyngeal activity) (Wellenberg et al, 2021b), CisPt disrupts dopaminergic behaviors (i.e. locomotion) in *C. elegans* and impairs mitochondrial function (Martinez-Fernandez et al., 2022). Although *C. elegans* seems to present a suitable model for studying the side effects of cAT, there are only a handful of studies that have actually used the nematode for addressing these types of questions. In addition to studies investigating the consequences of platinating agents with respect to neurotoxicity (Honnen et al., 2017; Martinez-Fernandez et al., 2022; Wellenberg et al., 2021a; Wellenberg et al, 2021b), the neurodegenerative effects of the CIPN-inducing drug paclitaxel on mechanosensory neurons have been investigated in *C. elegans,* too (Cirrincione and Rieger, 2020). Interestingly, similar to its toxic effect in human cells, paclitaxel stabilizes microtubules and inhibits cell division in *C. elegans* as well (Bajaj and Srayko, 2013), suggesting evolutionary conserved mechanisms. Another cAT, vincristine, has also been investigated exploiting *C. elegans* as a model. Hengartner et al. used *C. elegans* to identify factors involved in vincristine-induced apoptosis and identified *let-99* and its human ortholog *Depdc1* as relevant genes (Sendoel et al., 2014). Taken together, these studies demonstrate that cATs affect *C. elegans*, at least partially, in a manner that is comparable to humans.

In view of the claimed usefulness of *C. elegans* in neurotoxicity research, it is noteworthy that there are a couple of established methods to monitor sensory functions in *C. elegans* (Margie et al., 2013). This is important having in mind that CIPN in humans has been mainly characterized by sensory dysfunctions due to damage of dorsal root ganglions (DRG). Preliminary data of our own indicate that chronic treatment with high doses of CisPt reduces the nematode's chemotaxis towards diacetyl (not shown). Another argument for using *C. elegans* in basic and translational research in the field of cAT-induced neuropathy is that the nematode harbors a fully functional innate immune system. DNA damage in germ cells of *C. elegans* can trigger an innate immune response in the nematode that confers stress resistance (Ermolaeva et al., 2013). Similarly, CisPt increases the expression of *C. elegans* genes involved in innate immune responses (Garcia-Rodriguez et al., 2018). This is worthwhile to mention since DNA damage has recently been described to stimulate the innate immune system in eukaryotic cells as well (Tigano et al., 2021) and neuroinflammation is relevant for the development of CIPN (Fumagalli et al., 2020). Correspondingly, employing *C. elegans* to unravel the contribution of the innate immune system to cAT-induced CIPN can be anticipated to give meaningful results for the human situation.

Finally, many of the genes encoding HDACs, DNA repair and DDR factors in humans have homologous genes in *C. elegans* (Table 1). Most important, *C. elegans* harbors the majority of nucleotide excision repair (NER) genes, which is highly relevant having in mind that this DNA repair pathway is of particular relevance for the removal of CisPt-induced DNA lesions. Moreover, factors of DNA mismatch repair (e.g. MSH2, MSH6, MLH1) and DNA interstrand crosslink repair (e.g. FANCD2), which are other pathways of repair of CisPt-induced DNA damage (Koberle et al., 2010; Rabik and Dolan, 2007), are also largely conserved in *C. elegans* (Table 1). The same holds true for factors related to replicative stress responses (e.g. ATR, Chk1). These facts allow to dissect the contribution of different types of DNA damage and related DNA repair pathways as well as ATR/Chk1-related stress responses to the pathophysiology of DNA damage-related neuropathic mechanisms using the nematode as a meaningful model system. In addition, *C. elegans* harbors genes that are homologues to the majority of human HDACs (Table 1), and HDACi have similar effects on autophagy in both DNA repair compromised *C. elegans* and rodent models of Cockayne syndrome (Majora et al., 2018). This supports the view that the nematode is a particularly useful model system to examine the biological activities of HDACs and HDACi in the context of cAT-triggered neuropathy. Moreover, numerous nematode mutants and reporter strains are available (approx. 40,000 different strains are listed in WormBase and more than 22,000 *C. elegans* strains are available from the biggest *C. elegans* distributor, the Caenorhabditis Genetics Centre) and siRNA-mediated knock-down can be easily performed by feeding appropriate *Escherichia coli* harboring a plasmid containing gene-specific *C. elegans* genomic fragments between two inverted T7 promoters (Fraser et al., 2000; Kamath et al., 2001). These peculiarities of the *C. elegans* model substantially facilitate the genetic analyses of the molecular mechanisms contributing to cAT-mediated neuropathy in a multicellular organism.

Admittedly, *C. elegans* has also some limitations for studying the

Table 1
List of selected human DNA repair-, DDR- and HDAC-related genes and their homologous genes in *C. elegans*.

	Human	C. elegans		Human	C. elegans
DNA repair (BER)	*Ape1*	*exo-3*	**DNA repair (HR)**	*BRCA2*	–
	Fen1	*crn-1*		*BARD1*	*brd-1*
	Lig1	*lig-1*		*CtIP*	*com-1*
	Lig3	*K07C5.3*		*Mre11*	*mre-11*
	MPG	–		*MDC1*	–
	Mutyh	–		*NBS1*	–
	NEIL1,2,3	–		*RAD18*	–
	NTH1	*nth-1*		*RAD50*	*rad-50*
	OGG1	–		*RAD51*	*rad-51*
	PARP1	*parp-1*		*RAD52*	–
	PARP2	*tag-124*		*RAD54*	*xnp-1*
	PCNA	*pcn-1*		*RNF8*	–
	SMUG	–		*RNF168*	–
	TDG	–		*SKP2*	*skpt-1*
	UNG1	*ung-1*	**DNA repair (NHEJ)**	*Artemis*	–
	UNG2	–		*DNA-PKcs*	–
	Xrcc1	–		*KU70*	*cku-70*
DNA repair (NER)	*Csa*	*csa-1*		*KU80*	*cku-80*
	Csb	*csb-1, F53H4.6*		*Lig IV*	*lig-4*
	RNA Pol2	*ama-1,*		*XRCC4*	–
		rpb-2–12	**DNA repair (MMR)**	*Exo1*	*exo-1*
	RPA	*rpa-1, R03H10.6,7*		*Msh2*	*msh-2*
				Msh6	*msh-6*
	TFIIH	*xpb-1, xpd-1, gtf-2H1,3–5, cdk-7*		*Mlh1*	*mlh-1*
				Pms2	*pms-2*
			DNA repair (TLS)	*PolI*	–
	XAB2	*syf-1*		*Polb*	–
	XPA	*xpa-1*		*Pold*	*F10C2.4*
	XPC	*xpc-1*		*Pole*	*pole-1*
	XPE	–		*Polμ*	–
	XPF	*xpf-1*	**HDACs**	*HDAC1*	*hda-1,3*
	XPG	*xpg-1*		*HDAC2*	*hda-1*
	ERCC1	*ercc-1*		*HDAC3*	*hda-2*
DNA repair (MGMT)	Mgmt	*agt-1*		*HDAC4*	*hda-4*
				HDAC5	*hda-4*
DDR	*ATM*	*atm-1*		*HDAC6*	*hda-6*
	ATR	*atl-1*		*HDAC7*	*hda-4*
	ATRIP	–		*HDAC8*	–
	Chk1	chk-1, txt-2, kin-33,34		*HDAC9*	*hda-4*
				HDAC10	*hda-5,6,10*
	Chk2	chk-2, T08D2.7		*HDAC11*	*hda-11*
	FANCD2	fcd-2		*Sirt1*	*sir-2.1*
	FANCJ	dog-1		*Sirt2*	–
	FANCM	–		*Sirt3*	–
	HIPK2	*hpk-1*		*Sirt4*	*sir-2.2,2.3*
	MDM2	–		*Sirt5*	–
	PALB	–		*Sirt6*	*sir-2.4*
	p53	*cep-1*		*Sirt7*	–

adverse effects of cATs. For instance, the lack of detoxifying organs (e.g., liver or kidney), which are often affected by cATs as well, narrows the use of *C. elegans* for toxicological assessments. Moreover, human active pro-drugs might be overlooked having in mind that drug metabolism (phase I / phase II) is different in the nematode as compared to humans. Most important yet, intending to exploit *C. elegans* as a screening model to identify drugs useful to cope with chemotherapy-induced neurotoxicity, the lack of a blood-brain barrier in *C. elegans* is a crucial factor to consider, especially when central neurotoxicity of cATs is in focus. This is because the absence of such a barrier in the nematode allows substances to directly act on *C. elegans* neurons, whereas these compounds might not sufficiently pass the blood-brain barrier in humans. Therefore, using *C. elegans* might have a bias to produce false-positive hits. However, it is not only the lack of the blood-brain barrier that could be an obstacle. *C. elegans* is surrounded by a fairly impermeable cuticle that limits drug uptake by simple diffusion as compared to popular in vitro models. Drug uptake in *C. elegans* mainly depends on the pharynx pumping activity. A study on the uptake of substances showed that only 10% of test compounds are efficiently taken up by *C. elegans* (Burns et al., 2010). As a result, some relevant test substances may not affect the nematode due to poor uptake. To improve drug uptake, it might be useful to employ mutants with increased cuticular permeability (Xiong et al., 2017). In any case, the peculiarities of the nematode are the reason why the drug doses that need to be applied in *C. elegans* are usually higher than those clinically relevant for humans.

Nonetheless, currently available data are encouraging to exploit *C. elegans* as 3R conform in vivo model to further unravel molecular mechanisms of platin-induced neurotoxicity and, furthermore, to identify novel neuroprotective lead substances in large-scale compound screening approaches or to scrutinize the debated neuroprotective efficacy of candidate compounds such as the aforementioned DDR modifiers (i.e. ATM, ATR, Chk1/2, Wee1, HIPK2 inhibitors), HDACi and superoxide dismutase (SOD) mimetics. The latter have been already tested in *C. elegans*. So, the SOD mimetics EUK-8 and EUK-134 were shown to increase SOD activity, especially in mitochondria, and protect against oxidative stress in *C. elegans* (Keaney et al., 2004). Yet, their effects on the lifespan of *C. elegans* are controversially discussed (Keaney and Gems, 2003; Keaney et al., 2004; Melov et al., 2000). EUK-8, EUK-134 and other SOD mimetics are hypothesized to be effective in the treatment of ROS-induced neurodegenerative diseases in rodents (Rouco et al., 2020). For instance, they revealed neuroprotective effects in paraquat-induced loss of dopaminergic neurons (Peng et al., 2005) as

well as radiation-induced cognitive impairment (Raber et al., 2017). Surprisingly, the efficacy of SOD mimetics has not yet been tested with respect to neuroprotection in *C. elegans*. To summarize, we suggest the exploitation of the nematode to be very helpful for the identification and molecular characterization of novel SOD mimetics, DDR modifiers and HDACi which are designed to mitigate CIPN.

5. Conclusions

There is an obvious and urgent need for effective preventive and therapeutic strategies to combat CIPN. This requires both a detailed understanding of the key molecular mechanisms involved in cAT-induced neuropathy and, furthermore, appropriate assay systems to confirm the neuroprotective efficacy of pre-selected candidate drugs or to identify novel and effective drug candidates. Since it is rational to assume that the induction of DNA damage by cAT appreciably contributes to the pathophysiology of CIPN, we suggest targeting DNA damage-related stress responses by DDR-inhibitory compounds and HDACi as a reasonable neuroprotective strategy. In addition, having in mind that the majority of DNA repair- and DDR-related pathways, as well as HDAC, are well conserved in *C. elegans*, we suggest to integrate the nematode as a highly suitable 3R-compatible model organism into cAT-induced neurotoxicity research, aiming to improve the nowadays very limited pharmacological options to prevent and treat CIPN.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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