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REVIEW

Mechanisms and Management of Albumin-Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer

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Abstract: Breast cancer incidence continues to rise globally, with molecular subtyping now playing a critical role in prognosis and treatment selection. The main subtypes—Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC)—exhibit distinct clinical behaviors and treatment responses, with respective molecular characteristics. Chemotherapy plays a pivotal role in the comprehensive treatment of breast cancer, being widely used in neoadjuvant, adjuvant, and metastatic systemic therapy. Albumin-Paclitaxel based regimens remain the cornerstone of clinical treatment, particularly for highly aggressive subtypes like triple-negative breast cancer (TNBC) and HER2-positive breast cancer. However, 30–60% of breast cancer patients receiving chemotherapy develop chemotherapy-induced peripheral neuropathy (CIPN). Approximately 35% experience severe (≥grade 2) symptoms, often requiring dose modification or treatment discontinuation. Albumin-Paclitaxel's neurotoxicity primarily involves two mechanisms: microtubule stabilization disruption causing axonal transport impairment, and sensory neuron mitochondrial dysfunction. For younger patients, this presents dual clinical challenges: controlling tumor progression while managing neuropathic pain and functional impairment that significantly affect quality of life and work capacity. Treatments are constantly evolving and currently, the most effective treatments (eg duloxetine, cold therapy). Understanding CIPN pathogenesis, diagnostic approaches, and developing effective prevention/treatment strategies is clinically crucial. This maintains treatment adherence and efficacy while improving long-term quality of life for breast cancer patients.

Keywords: nab-paclitaxel, peripheral neuropathy, breast cancer, mechanism, treatment

Background

Breast cancer is one of the most common malignancies in women worldwide, representing approximately 30% of all malignancies,[1] and the incidence is increasing at a rate of 2% per year.[2,3] The main subtypes—Luminal A (ER+, PR+, HER2 −/1+, KI-67<20%), Luminal B (ER+/PR±, HER2 -/1+/2+/3+, KI-67>20%), HER2-enriched (ER−/PR−, HER2 -), and triple-negative breast cancer (TNBC:ER−/PR−, HER2 −)—exhibit distinct clinical behaviors and treatment responses.[4] Most breast cancer patients need to undergo chemotherapy, and the commonly used chemotherapeutic drugs for breast cancer include anthracyclines, paclitaxel, cyclophosphamide, and albumin-bound paclitaxel (hereinafter "Albumin-Paclitaxel").[5]

Since the discovery of paclitaxel, research on taxane-based drugs has undergone over five decades of development,[6] clinically utilized paclitaxel agents primarily include paclitaxel injection, docetaxel, paclitaxel liposome, and nab-paclitaxel. The arrival of these drugs has greatly boosted the survival rates of cancer patients. Paclitaxel has significantly improved cancer survival rates, but often induces short- and long-term adverse effects. Compared with conventional paclitaxel, nab-paclitaxel and liposomal paclitaxel demonstrate reduced systemic toxicity. This advantage stems from their optimized drug delivery systems.

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However, Albumin-Paclitaxel induces neurotoxicity more rapidly than conventional paclitaxel, often resulting in chemotherapy-induced peripheral neuropathy (hereinafter referred to as CIPN), although the overall incidence rates are comparable. Younger patients face dual challenges: controlling tumor progression and managing neuropathic complications. These complications include functional impairment that severely reduces quality of life and work capacity. Therefore, in-depth investigation into the etiology of peripheral neuropathy, particularly the molecular mechanisms underlying CIPN caused by Albumin-Paclitaxel, holds profound clinical significance for optimizing therapeutic strategies and improving patient prognosis.

Peripheral neuropathy refers to injury, inflammation, or degeneration of peripheral nerve fibers, characterized by numbness, tingling, or burning sensations in the hands and feet that may spread to the limbs. It can cause severe pain, extreme sensitivity to touch, lack of coordination, muscle weakness, and paralysis if motor nerves are affected.[7] Symptoms usually present as a typical "glove-and-sock" neuropathy, and in severe cases, these symptoms develop into sensory loss. Motor symptoms occur less frequently than sensory symptoms, often presenting as distal weakness, gait and balance disturbances, and impaired movement, which exert a significant and frequently underappreciated effect on QoL. The mechanisms underlying Albumin-Paclitaxel-induced chemotherapy-induced peripheral neuropathy (CIPN) may primarily be associated with its specialized drug delivery system and neurotropism, which will be elaborated in subsequent sections.

Risk factors for CIPN may also include advanced age, underlying comorbidities (eg, diabetes mellitus, hyperthyroidsm, and obesity), unhealthy lifestyle habits (such as smoking and alcohol abuse), and history of neurological disorders.[8] Notably, Albumin-Paclitaxel is among the chemotherapeutic agents most frequently associated with CIPN. The incidence of peripheral neuropathy is higher with paclitaxel and Albumin-Paclitaxel than with docetaxel, and the overall incidence of peripheral neurotoxicity with albumin-paclitaxel is 57%–83%, and is manifested in 2–33% of patients. Investigators have uncovered neurotoxicity caused by high-dose (250 mg/m²) paclitaxel in 50% of patients within nine months of withdrawal.[9,10] Compared with conventional paclitaxel formulations, Albumin-Paclitaxel and liposomal paclitaxel demonstrate superior overall safety profiles due to their optimized drug delivery systems. However, significant differences in neurotoxicity were observed among the three formulations: although liposomal paclitaxel reduces overall adverse effects, it exhibits a higher incidence of short-term neuropathy compared to conventional paclitaxel; while Albumin-Paclitaxel shows comparable overall neurotoxicity rates to conventional paclitaxel, its neurological symptoms manifest earlier and progress more rapidly. Clinical data indicate that the median recovery time from severe neurotoxicity induced by Albumin-Paclitaxel was 22 days after treatment discontinuation.[11]

Albumin-Paclitaxel serves as an important therapeutic agent for breast cancer, showing notable clinical benefits especially in the neoadjuvant chemotherapy setting where it achieves substantially higher pathological complete response rates compared to conventional taxanes. This leads to better surgical outcomes and improved patient survival. However, this agent induces chemotherapy-induced peripheral neuropathy earlier than other taxanes, significantly affecting patients' quality of life. Given this important clinical challenge, research into the molecular mechanisms behind nab-paclitaxel-induced neuropathy, development of accurate neurotoxicity evaluation methods, and investigation of effective prevention and management approaches carries significant clinical and social value. These efforts are crucial for advancing precision medicine, improving treatment effectiveness, and reducing patient suffering.

Molecular Mechanisms Underlying Peripheral Neuropathy Induced by Albumin-Paclitaxel

Although nab-paclitaxel can induce CIPN, its pathophysiological mechanisms have not been fully elucidated. Neurotoxic substances induce axonal polyneuropathy through multiple pathways, with the primary mechanisms involving microtubule disruption and mitochondrial dysfunction. Additionally, these substances may trigger cytokine-mediated alterations in pain mediators (eg, growth factors), interfere with ion channel function, and induce cytotoxic DNA damage.[12,13] This review summarizes the following potential pathogenic mechanisms:

Structural Disorders of Microtubules

The basis for the ability of microtubules to perform important functions within cells lies in their tubular structure. Microtubules are unbranched hollow tubules composed of tubulin, with an inner diameter of 14–15 nm and an outer diameter of 22–25 nm.[14] α-Tubulin and β-tubulin are the major proteins that comprise microtubules, and the heterodimers formed by α and β tubulin are the basic units that constitute microtubules. The α/β fibrils are formed in the configuration of a dimer, with the fibrils closed to form a tubular structure. Microtubules are composed of α-tubulin and β-tubulin, which are the primary protein subunits. These subunits form heterodimers, with one α-tubulin and one β-tubulin pairing together. During microtubule assembly, these heterodimers polymerize in a head-to-tail manner to form linear protofilaments. This process can be likened to creating a string of beads, similar to the structure of a traditional Chinese "sugar hulu" (a skewered candy treat).

Once these protofilaments are formed, 13 of them align laterally and interact with each other to create a closed, hollow tube. This arrangement ensures that the microtubule is structurally stable and capable of fulfilling its diverse cellular functions. When viewed in cross-section, a microtubule appears as a ring composed of 13 parallel protofilaments.[14]

Microtubules play an important role in maintaining cell morphology, regulating cellular division, in organellar localization and cell function, and signaling and material transmission. The dynamic balance of microtubules is crucial for the normal activities of cells, and the anticancer drug taxol can bind to the α/β heterodimer protein assembly that is required to reduce the concentration of tubulin, promote the assembly of microtubules and abnormally stable microtubules, destroy the normal dynamic balance of microtubules, and cause fatal damage to cells. Paclitaxel is a drug type that promotes tubulin polymerization, suppresses tubulin depolymerization, interferes with the formation of the mitotic spindle, and induces cellular arrest and apoptosis, thereby exerting anticancer effects.[15]

Impaired Mitochondria in Neurons and Non-Neuronal Cells

Mitochondria are highly dynamic, complex organelles that principally provide energy but also play key roles in cell death, signaling pathways, apoptosis, reactive oxygen species (ROS) production, and calcium homeostasis—all of which are disturbed in neurodegeneration.[16] Neurons are heavily dependent on mitochondria and are susceptible to mitochondrial dysfunction due to their complex morphology and high metabolic requirements. Neuronal dysfunction is a core feature of neurodegenerative diseases and is therefore closely related to mitochondrial dysfunction.

Mitochondria play a critical role in energy metabolism and free-radical metabolism. Whether in neuronal or non-neuronal cells, mitochondrial damage leads to oxidative stress and the production of ROS such as hydroxyl radicals, peroxides, superoxides, and singlet oxygen. Paclitaxel is able to induce mitochondrial swelling, vacuole formation, and structural loss; and abnormal mitochondrial functions are pivotal to the development of CIPN.[17] Impairing axonal transport of lipids, proteins, ion channels,[18] and mRNA[19] to the distal neuronal fraction may exert a major impact on this process. Increased levels of ROS are also detected in sensory neurons and the spinal cord,[20–22] and increases in ROS levels lead to activation of the apoptotic process, disruption of cytoarchitecture, and nerve demyelination. These events lead to impaired signaling and activation of immune processes, including the increased release of proinflammatory cytokines that can lead to the development of peripheral neuropathy.

Calcium Imbalance in the Internal Environment

Impairment of mitochondrial physiologic functions may affect calcium-signaling pathways and promote further pathologic functional and structural changes in neurons and glial cells. Mitochondria and endoplasmic reticulum (ER) serve as intracellular stores of Ca^{2+} and must maintain their integrity. Ca^{2+} homeostasis is crucial since intracellular alterations in Ca^{2+} concentrations may affect membranal excitability, neurotransmitter release, and gene expression in neurons and glial cells.[23] Increasing concentrations of intracellular Ca^{2+} may lead to the activation of calpain (a potent protease), resulting in unregulated proteolysis, directly triggering axonal degeneration.[24] The chelation of extracellular Ca^{2+} ions leads to increased Na^{+} conductance, decreased threshold potential, and membrane resistance,[25] leading to early stages of cold allodynia rather than late mechanical allodynia.[26] Activation of protein kinases and caspases by chemotherapeutic

agents may also lead to damage of intracellular structures. Cisplatin and oxaliplatin can induce MAPK-associated apoptosis in dorsal root ganglion (DRG) neurons, and MAPK inhibitors prevent platinum-induced DRG damage in vitro.[27]

Albumin-Paclitaxel are able to activate the mitochondrial permeability transition pore (mPTP) and lead to rapid mitochondrial depolarization, interfering with Ca^{2+} release from the mitochondria and ER,[28] further leading to neuronal damage. Moreover, pathologic changes such as modulations of peripheral nerve excitability, immune processes, and neuroinflammation, and alterations in dorsal root ganglia[29] can lead to sensory dysfunction and pain and participate in the development of CIPN.

Dysregulation of Ca2+ has been shown to play a role in the pathogenesis of CIPN.[30] Misregulation of intracellular Ca2+ in neuronal and non-neuronal cells was observed in paclitaxel neuropathy models.[31,32] Paclitaxel activates mitochondrial Ca2+ release, a process likely mediated via the activation of the mPTP, lead to rapid mitochondrial depolarization.[33] Paclitaxel may also stimulate the release of Ca^{2+} from the ER, with the process potentially mediated by the 1,4,5 inositol triphosphate receptor (IP3R),[34,35] resulting in increased expression of the Ca V 3.2 channel in rats, when this channel is inhibited.

Axonal Degeneration

Taxanes have been shown to cause direct peripheral nerve damage, nerve fiber loss, and the occurrence of demyelination.[36] Neural fiber types can be divided into fine fibers and crude fibers. Fine fibers, which are the cytoskeletal components dominated by microtubules, are unmyelinated, with the function of regulating pain and temperature, showing self-discipline. Crude fibers are the cytoskeletal elements innervated by neurofilaments, which are characterized by myelinated, innervated, and vibratory proprioception.

Direct peripheral nerve damage, nerve fiber loss, and demyelination have been reported in various studies.[37] Disruption of microtubules and the resulting impairment in axonal transport of important cellular components elicit the degeneration of distal nerve segments (Wallerian degeneration) and axonal membrane remodeling[38] in a rodent model of taxol-induced CIPN (Boyette et al). Zhang et al showed in rodent models that reduced levels of the chemokine MCP1/CCL-2 reduced neurodegeneration and CIPN behavior.[39] Axonal transport is easily affected by changes in the cell structure, but how exactly paclitaxel influences this process is still unclear. It's also wrong to think that one simple effect explains everything about how paclitaxel impacts transport. Problems with transport might just be one part of why paclitaxel causes nerve damage. When it comes to repairing nerve damage in distal peripheral neuropathy (DPN), the process takes longer because it involves both segmental demyelination and axonal degeneration. DPN mainly promotes axon regrowth and nerve recovery by boosting the production of nucleic acids, proteins, and phospholipids in nerve cells.

Functional Changes in Ion Channels

In the taxol-induced CIPN model, reduced expression of K^+ channels causing spontaneous activity of the nociceptors was observed in the DRG,[40] and activation of the cation channels TRPV 1 and TRPA 1 (important components of pain signaling) was detected in DRG neurons.[41,42] And antagonists of TRPA 1 have been shown to relieve paclitaxel-induced inflammation, abnormal cold pain, and hyperalgesia.[43] Paclitaxel treatment augmented the number of NaV channels, which may have accounted for the development of CIPN.[44,45] Gheraldin et al[46] showed that blocking this channel alleviated hyperalgesia in rats. Altered expression and function of ion channels (NaV, KV, and TPR) is thus another mechanism that promotes the development of CIPN.

Immune Processes and Neuroinflammation

Paclitaxel stimulates increased production of proinflammatory cytokines (tumor necrosis factor (TNF)-α and IL-1 β) and decreases the production of anti-inflammatory cytokines (IL-4 and IL-10).[20,47] This process then attracts and activates immune cells and engenders the development of neuroinflammation.[48] Krukowski et al[49] showed that IL-10 attenuated paclitaxel-induced CIPN. Paclitaxel also leads to microglial and astrocyte activation in DRG,[50,51] and augments macrophage numbers and peripheral nerves.[52] Inhibition of macrophages and microglia additionally prevented the development of mechanical hyperalgesia and loss of epidermal nerve fibers.[53] Release of cytokines stimulates the

TLR 4 receptor in DRG cells and blocking this receptor reduces pain behavior in mice.[54] In addition to cytokines, the release of other inflammatory molecules such as prostaglandins (PGs) and leukotrienes also mediate inflammation, neutralizing invading pathogens and allowing tissue repair, and provoking peripheral neuralgia.

The pathogenesis of peripheral neuropathy involves multiple interrelated molecular mechanisms, including microtubule dysfunction-induced impairment of axonal transport, oxidative stress-mediated neuronal injury, neuroimmune activation driven by inflammatory mediators, and aberrant electrical signaling due to ion channel abnormalities.[55] These interconnected pathological processes collectively disrupt the structural and functional integrity of the peripheral nervous system, ultimately manifesting as clinical symptoms such as sensory disturbances and neuropathic pain (Figure 1). Elucidating these pathological mechanisms not only provides critical molecular markers and biological rationale for clinical evaluation, but also establishes a theoretical foundation for developing precision therapeutic strategies targeting microtubule stabilization, antioxidation, anti-inflammation, and ion channel modulation. Based on these mechanistic

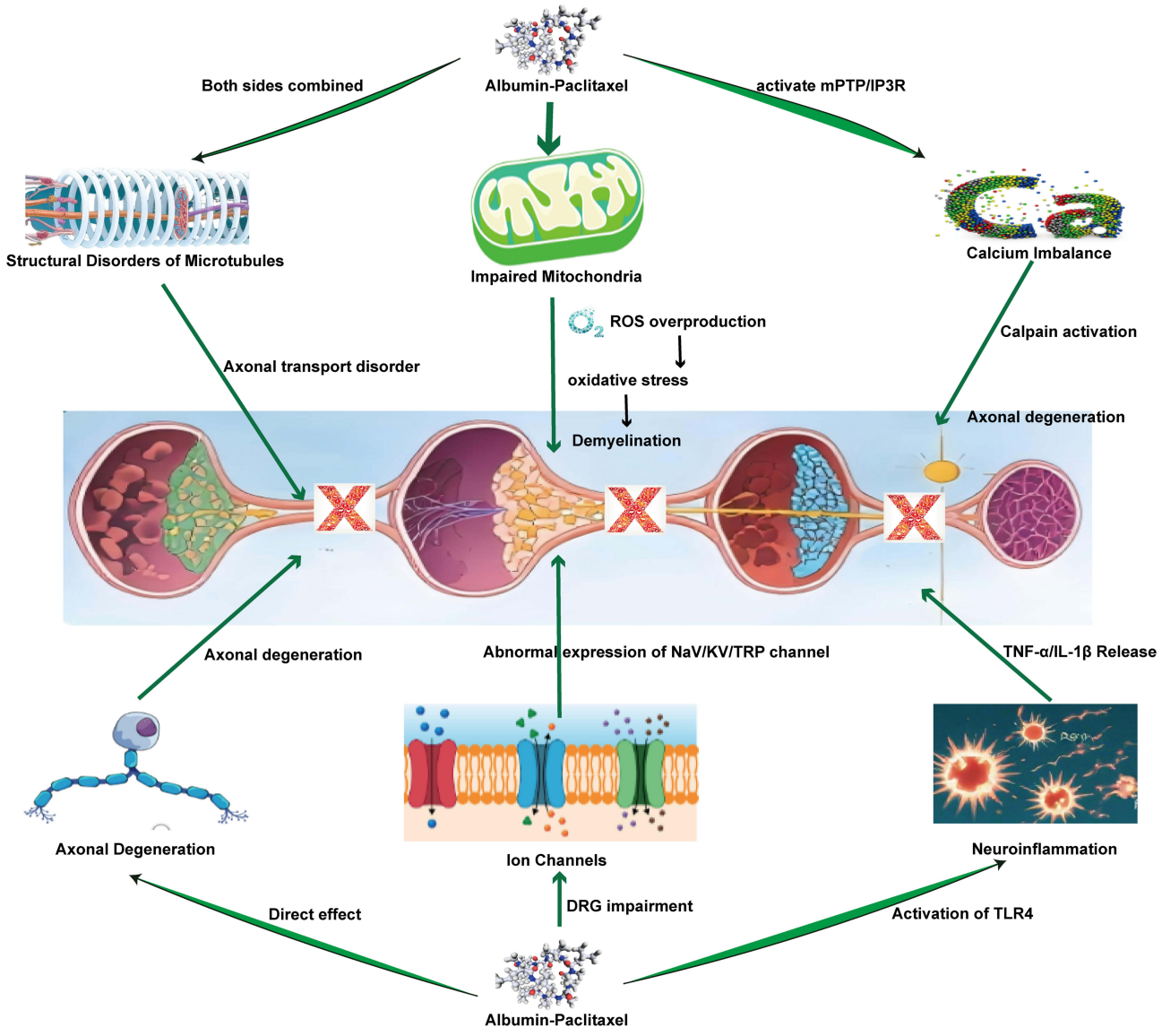

Figure 1 Mechanisms of Albumin-Paclitaxel-Induced Peripheral Neuropathy. This figure illustrates the key molecular mechanisms underlying Albumin-Paclitaxel-induced peripheral neuropathy. Albumin-Paclitaxel activates the mitochondrial permeability transition pore (mPTP) and inositol triphosphate receptor (IP3R), triggering a cascade of pathological events: structural disorders of microtubules impair axonal transport; mitochondrial dysfunction leads to reactive oxygen species (ROS) overproduction; calcium imbalance activates calpains; and these processes collectively induce axonal degeneration, demyelination, abnormal expression of ion channels (NaV, KV, TRP), and release of proinflammatory cytokines (TNF-α, IL-1β). These interconnected pathways ultimately contribute to neuroinflammation and peripheral neuropathy.

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insights, the following sections will systematically review current clinical assessment approaches and recent therapeutic advances in peripheral neuropathy.

Evaluation of Peripheral Neuropathies

The neurological symptom score (NSS) and neurological disability score[56] (NDS) are simple screening methods that have a history of application. The NSS is designated according to symptoms, location, duration, and pain relief; the NDS is defined according to the ankle reflex, toe vibrations, acupuncture, and temperature for signs of moderate or severe neuropathy (ie, with moderate or severe neuropathy scored as 6 points, with NDS from 3 to 5 points or NSS to 5 points).[57] The NSS/ NDS scoring system exhibits good applicative value for patients with severe neurologic symptoms and neurologic defects. Other neurologic rating scales are the Michigan Neuropathy Screening Instrument (MNSI),[56] Michigan Diabetic Neuropathy Score (MDNS),[58] the Toronto Clinical Scoring System (TCSS),[56] the numerical rating score (NRS), and the visual analogue scale (VAS) are used to assess pain changes.

In our clinical practice, we have instead applied a convenient and effective evaluation. The patient assessment scale for nab-paclitaxel-induced peripheral neuropathy includes methods such as the Evaluation Criteria for Common Adverse Events (National Cancer Institute-Common Terminology Criteria for Adverse Events, NCI-CTCAE) (Table 1).[59] The National Cancer Institute (NCI) of the National Institutes of Health (USA) issued a standardized definition of adverse events called the Common Terminology Standard for Adverse Events, also known as the General Toxicity Standard (common toxicity criteria, CTC) to describe the severity of organ toxicity in cancer patients. The Total Neuropathy Score (TNS) developed by Johns Hopkins University (Table 2),[59] is a comprehensive scale (0–40) score that combines symptom scores with objective scores of sensory deficits and neuro electro physiologic parameters. The Patient

Table 1 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE)

Clauses and Subclauses	Level 1	Level 2	Level 3	Level 4	Level 5
Sensory neuropathy	Asymptomatic; loss of tendon reflexes or sensory abnormalities (including tingling sensation) without affecting body function	Sensory changes or abnormalities (including tingling sensation) that affect limb function but not daily life	Sensory changes or abnormalities (including tingling sensation) that affect daily life	Functional incapacitation	Die
Motor neuropathy	Asymptomatic; weakness identified only by diagnostic examination	Symptomatic weakness affecting physical function but not daily life	Weakness affecting daily life, including walking	Life-threatening; loss of function	Die

Notes: The grading criteria are based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), which standardizes the assessment of adverse event severity in oncology clinical practice.
Abbreviation: NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

Table 2 Total Neuropathy Score

Clauses and Subclauses	0 Points	1 Points	2 Points	3 Points	4 Points
Sensory neurological symptoms	Not present	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist joint	Symptoms extend to knee or elbow joint	Symptoms extend above knee/ elbow joint or affect function
Motor nerve symptoms	Not present	Mild motor difficulties	Moderate motor difficulty	Assistance required for activities	Paralysis
Number of autonomic symptoms	Not present	1 symptom	2 symptoms	3 symptoms	4 or 5 symptoms
Sensitivity (needle aspiration)	Normal	Reduced in fingers and/or toes	Reduced below wrist and/or ankle	Reduced below elbow and/or knee	Reduced above elbow and/or knee

(*Continued*)

Table 2 (Continued).

Clauses and Subclauses	0 Points	1 Points	2 Points	3 Points	4 Points
Vibration perception sensitivity	Normal	Reduced in fingers and/or toes	Reduced below wrist and/or ankle	Reduced below elbow and/or knee	Reduced above elbow and/or knee
Muscle strength	Normal	Mild weakness (strength grade 4)	Moderate weakness (strength grade 3)	Severe weakness (strength grade 2)	Paralysis (strength grade 0–1)
Tendon reflexes	Normal	Ankle reflexes attenuated	Ankle reflexes absent	Ankle reflexes absent + other reflexes attenuated	All reflexes absent
Sural nerve sensory amplitude	Normal/<5% decrease from LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN
Common peroneal nerve amplitude	Normal/<5% decrease from LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN
[Note: Clarify parameter]	Normal to 125% of ULN	126–150% of ULN	151–200% of ULN	201–300% of ULN	>300% of ULN

Abbreviations: LLN, the lower normal limit; ULN, the upper normal limit.

Assessment scale used to assess nab-paclitaxel-induced peripheral neuropathy includes the Neurotoxicity Assessment Scale in gynecological tumor patients (functional assessment of cancer therapy, FACT) (Table 3).[59]

Magnetic resonance imaging/diffusion tensor imaging (MRI/DTI) enables direct visualization of structural abnormalities in peripheral nerves (eg, nerve hypertrophy, demyelination), demonstrating particular utility in evaluating radiculopathy or plexopathies. Its quantitative assessment of fiber tract integrity facilitates early detection of microscopic damage.[60] High-resolution ultrasonography provides real-time dynamic imaging with high sensitivity for evaluating morphological changes, vascularity, and entrapment of superficial nerves (eg, common peroneal nerve).[61] Positron emission tomography-computed tomography (PET-CT) indirectly assesses neuroinflammatory activity through glucose metabolism tracers (eg, ^{18}F-FDG). However, its clinical application requires further validation due to cost constraints and

Table 3 Functional Assessment of Cancer Therapy, FACT

Symptom	Not Have (0)	Mild (1)	Obvious (2)	Severe (3)	Very Severe (4)
Numbness or tingling in hands	0	1	2	3	4
Numbness or tingling in feet	0	1	2	3	4
Discomfort in hands	0	1	2	3	4
Discomfort in feet	0	1	2	3	4
Pain or muscle spasms	0	1	2	3	4
Sensation of weakness	0	1	2	3	4
Hearing difficulty	0	1	2	3	4
Tinnitus	0	1	2	3	4
Difficulty fastening buttons	0	1	2	3	4
Inability to identify small object shapes by touch	0	1	2	3	4
Walking difficulty	0	1	2	3	4

Notes: Grade 0 is 0; Grade 1 is 1–4; Grade 2 is 5–8; Grade 3 is 9–14.
Abbreviation: FACT, Functional Assessment of Cancer Therapy.

limited research data.[62] The sympathetic skin response (SSR) precisely detects autonomic dysfunction and is particularly valuable for auxiliary diagnosis of diabetic or chemotherapy-induced neuropathy.[63] Additionally, electroencephalography (EEG) offers unique advantages in monitoring abnormal discharges associated with central neurotoxicity.[64] Furthermore, the artificial intelligence (AI) model proposed by Guo et al[65]—which integrates electrophysiological, radiological, and clinical data—demonstrates potential for enhancing diagnostic efficiency. However, additional clinical validation remains necessary. Future research directions should prioritize multimodal imaging fusion and the combined analysis of biomarkers with imaging parameters to untangle the pathophysiological mechanisms underlying chemotherapy-induced peripheral neuropathy.[66]

Treatment Plan

Although the current evaluation methods are relatively comprehensive, therapeutic strategies still face significant challenges. Clinical experience indicates that albumin-paclitaxel-induced neuropathy is a more difficult problem to solve due to the lack of effective prophylactic or therapeutic agents.[67] CIPN has two main aspects with respect to harm to the patients. One is that it can affect the QoL of cancer survivors, and, two, it can also lead to dose reduction, early termination of drugs, or even poor treatment cessation. Therefore, it is of paramount importance to relieve the peripheral neuropathy or other radical side effects in patients.

Neurotrophic drugs are usually used to prevent and improve symptoms; these include amifostine, glutamine, acetyl l-carnitine, and vitamin E. Drugs commonly used for the symptomatic treatment of neuropathic pain include various opioids, tricyclic antidepressants, anticonvulsants, serotonin reuptake inhibitors (SSRI class I), and nonsteroidal anti-inflammatory drugs (NSAIDs).[68]

Several studies have been conducted to prevent and treat TIP but clinical data remain controversial; and some alternatives and treatment adjustments (see below) can appropriately limit neurotoxicity, but additional clinical data are needed to further demonstrate efficacy.

Neuroprotective Drugs

Axonal transport is easily affected by changes in the cell structure, but how exactly paclitaxel influences this process is still unclear. It's also wrong to think that one simple effect explains everything about how paclitaxel impacts transport. Problems with transport might just be one part of why paclitaxel causes nerve damage. When it comes to repairing nerve damage in distal peripheral neuropathy (DPN), the process takes longer because it involves both segmental demyelination and axonal degeneration. DPN mainly promotes axon regrowth and nerve recovery by boosting the production of nucleic acids, proteins, and phospholipids in nerve cells. Methyl cobalamin is commonly used clinically (also called mecobalamin), deriving from vitamin B12, and has the active effect of vitamin B12 in promoting the formation of nerve myelin and stimulating the regeneration of damaged axonal cells through the blood-cerebrospinal fluid barrier, increasing the activity of the neurotransmitter acetylcholine, improving nerve conduction velocity, and ameliorating nervous tissue transmission disorders and metabolic disorders.[69] Mecobalamin can effectively relieve limb pain and numbness in patients, and can improve neuro polyol to a certain degree, which has been widely recognized in the treatment of DPN. Other drugs such as neurotrophin, C peptide, inositol, ganglioside ester, and linolenic acid have also shown clinical effects in recent years.

Erythropoietin (EPO) is a cytokine involved in the regulation of hematopoiesis, and demonstrates neuroprotective effects such as enhancing nerve regeneration and recovery after peripheral nerve injury.[70,71] Since chemotherapeutic agents are postulated to induce peripheral neuropathy by damaging peripheral nerves, EPO's neuroprotective effect makes it an ideal candidate for CIPN.[72] However, the use of EPO for CIPN is highly contraindicated and should be treated with caution as EPO is associated with tumor cell growth.[73]

Tricyclic Drugs and Other Antidepressants

This class of pharmaceuticals includes duloxetine, amitriptyline, drug of pyrazine, and the new antidepressant escitalopram. Such drugs not only relieve patient pain but also improve anxiety and depression to a certain extent. Their side effects are mainly dry mouth and drowsiness; and they may also induce postural hypotension.[74] Duloxetine can be used

in the initial treatment of DPN pain, and it exerts an obvious analgesic effect on the pain caused by DPN. The dose can be gradually increased from low to high according to the needs of the condition, with good efficacy.

The American Society of Clinical Oncology (ASCO) guidelines suggest that duloxetine is the best candidate for neuropathic pain associated with CIPN.[75]

Amitriptyline is effective for treating painful diabetic neuropathy and post - herpetic neuralgia, and may also confer benefits in other neuropathic pain syndromes. However, it should be used cautiously in patients with an elevated risk of adverse events.[76] Carbamazepine, a representative drug of pyrazine - class medications, is an anticonvulsant or anti - epileptic agent. It is also utilized for treating peripheral neuropathy (nerve pain induced by diabetes) and trigeminal neuralgia (facial nerve pain). Its mechanism of action involves reducing abnormal brain electrical activity or aberrant nerve impulses.[77] According to the study by Ovlyakulov et al, the new antidepressant escitalopram shows moderate superiority over citalopram in suppressing neuroinflammation, preventing dopaminergic neuronal death, and alleviating motor discoordination in 6-OHDA-induced Parkinson's disease mice.[78]

Opioid Drugs and Non-Opioid Analgesics

Tramadol, oxycodone, and capsaicin can be prescribed if patients have not received satisfactory treatment following first-line drugs, but due to their addictive properties and the risk of other complications, tramadol and other opioids as first-line drugs for the treatment of DPN pain are not promoted in clinical practice. Capsaicin is principally used for the treatment of patients with limited pain sites. It is mediated by special molecular receptors on the primary afferent nerve terminals and cell membrane to reduce the release of pain substances and achieve analgesic effects.

Drugs Used to Improve Metabolic Disorders

Drugs that improve metabolic disorders act by reversibly inhibiting aldose reductase, the amino hexose pathway, and angiotensin-converting enzyme. These medications are currently commonly used, as are members of a new generation of aldose reductase inhibitors that can significantly inhibit the activity of aldose reductase and thus block polyol metabolic bypass; reduce the accumulation of sorbitol and fructose in nerve cells; reduce the damage to nerve cells; and prevent peripheral nerve edema, necrosis, and demyelination.[79] Epalrestat can improve the symptoms and signs of peripheral neuropathy in patients, and exerts actions on limb terminal nerve disorders, sensory abnormalities, and cardiac anomalies.[80]

Ion-Channel Blockers

Lidocaine is a sodium ion channel blocker that prevents the flow of sodium ions through the channel pore, and is effective in relieving neuropathic pain from various causes, including CIPN.[81] Intravenous (IV) lidocaine produced a significant, moderate long-term (a mean of 23 days) analgesic effect in eight of nine patients with CIPN.[82,83] These results[84] are very promising, and the most common adverse effect associated with intravenous lidocaine only comprised irritation at the injection site. To overcome this side effect and possibly increase the expected duration of relief, oral sodium channel blockers such as Merclaw can replace intravenous lidocaine.[85]

Infusion of magnesium ion has also been considered as a potential therapeutic option for CIPN, as investigators found a direct negative correlation between magnesium intake and CIPN severity. Magnesium supplementation during chemotherapy is designed to reduce neuronal hyperexcitation and global neuronal damage caused by oxaliplatin, and increased magnesium administration is associated with a lower prevalence of CIPN and milder symptoms in individuals experiencing CIPN.[86] However, other studies have failed to demonstrate any efficacy of using magnesium infusion for CIPN.[87] Similarly, calcium infusion failed to reduce CIPN in numerous studies, including those where combined calcium and magnesium infusion was expected to achieve additive effects.[88]

Gabapentin is an aminobutyric acid derivative that can combine with tubulin subunits to produce analgesic as well as anticonvulsant and anxiolytic effects, and can be used to treat mechanical hyperalgesia as well as other specific abnormal pain disorders.[89] This treatment can effectively improve patients' pain and exhibits significant effects on the treatment of multiple pain syndromes. Therefore, this drug is mostly applied in the treatment of neuropathic pain, achieving a favorable effect on peripheral nerve pain.[90] Correlation analysis showed that pregabalin reduced the influx of calcium

ions, inhibited the release of excitatory neurotransmitters such as glutamate, and suppressed pain perception in nerve injury and allergic pain.

Anti-Inflammatory Drugs

Some studies have shown that the optimal treatment for CIPN was NSAIDs, which can reduce pain symptoms and the underlying inflammation associated with pain.[91] The release of inflammatory factors by inflammatory cells (eg, TNF-α, IL-1, and IL-6) is closely related to the occurrence of neuropathic pain, and their increase was positively correlated with pain severity.[92] Clinical anti-inflammatory drugs are based on their inhibition of cyclooxygenase-2 (COX-2) activity, which can prevent the production of inflammatory PGs and achieve antipyretic, analgesic, and anti-inflammatory effects.[93] Studies have revealed that celecoxib treatment effectively relieved the onset of cancer pain without increasing the risk of gastrointestinal and cardiovascular disease, and reduced to a degree the adverse reactions caused by opioids.[94] Anti-inflammatory painkillers work differently from corticosteroids due to their chemical makeup and unique way of reducing inflammation. This difference is why they are called NSAIDs. Patients often deal with many short-term and long-term bad reactions during treatment, which greatly lower their quality of life. They prevent the synthesis of PGs by inhibiting the activity of cyclooxygenase (COX) necessary for the synthesis of PGs, and exert antipyretic, analgesic, and anti-inflammatory pharmacologic effects.

Antioxidants

One of the mechanisms underlying CIPN action is the increased production of ROS in patients undergoing chemotherapy, and augmented levels of ROS can elicit direct nerve damage through enhanced oxidative stress. Moreover, some chemotherapeutic agents precipitate the depletion of certain elements, making nerves more vulnerable to damage (eg, glutathione), leading to neurotoxicity.[95] Although the mechanism of action underlying calmangafodipir treatment of CIPN has not been fully elucidated, studies suggest that its antioxidant properties may be neurologic and/or myelin protective, and prevent ROS-mediated injury.[96] Calmangafodipir also acts as a superoxide dismutase (SOD) analog with catalase and glutathione reductase-like properties.

Cold Therapy

According to an analysis of 1725 Danish patients, the incidence of peripheral neuropathy was significantly reduced with the application of ice gloves and socks during treatment (OR = 0.56; 95% CI, 0.38–0.81).[97] Authors of another multicenter clinical trial analyzed the effect of surgical gloves (SG), comparing the incidence of peripheral neuropathy with or without a suitable small-size surgical glove, and showed that the use of an SG significantly reduced hand neurotoxicity compared with the control hand (sensory neuropathy, 21.4% vs 76.1%; motor neuropathy, 26.2% vs 57.1%, respectively).[98] In addition, a summary of one study that encompassed 16 sites and published at the 2018 San Antonio Breast Cancer Symposium also confirmed a significant reduction in CIPN incidence in patients treated with ice gloves/socks.[99] In conclusion, wearing ice gloves and socks before and during chemotherapy should achieve a beneficial effect.

Acupuncture Treatment

Zhao et al[100] showed that acupuncture treatment improved the ion- distribution concentration in muscle and nerve blocks in patients with chemotherapy-induced peripheral neuropathy, thus increasing the antioxidant capacity of body-associated neurons. Acupuncture can also promote the energy-quantitative metabolic activity of the body's neuronal cells. It not only reduces the damage and proapoptotic effects of free radicals on the cellular structure and function of body neurons via an oxidative stress response, but also improves the microenvironmental state of the peripheral neuronal cells, promotes the recovery of neuronal cell tissue metabolism, facilitates the repair of toxic damage caused by chemotherapeutic agents, and improves a patient's clinical symptoms. Warm acupuncture benefits meridian collaterals, blood circulation qi, cold and dampness, warm stimulation of sun points,[101] Acupuncture points selected include Zusanli (ST36), Shousanli (LI10), Yanglingquan (GB34), Qihai (CV6), Fenglong (ST40), Waiguan (TE5), Quchi (LI11), and Taichong (LR3). After acupuncture, needles are retained at Zusanli (ST36), JieXi (ST41), Waiguan (TE5), and Yanglingquan (GB34). Some studies have shown that warm acupuncture therapy can effectively regulate the body's

visceral Yin and Yang balance, alleviate the clinical symptoms of peripheral neuropathy, and significantly relieve patients' pain, numbness, and discomfort.[101]

Additionally, Xiaoming ZHAO treated peripheral neuropathy using electroacupuncture combined with moxibustion, primarily selecting the acupoints Zusanli (ST36), bilateral Xiexi (ST41) of the upper limbs, Hegu (LI4), and Guanyuan (CV4); meanwhile, acupuncture combined with moxibustion at Zusanli (ST36) was used as an adjunctive treatment.[100] After two courses of treatment, the incidence of peripheral neuropathy in the observational group patients was only 50%, 90% lower than in the control group of patients; and in the observational group of patients after chemotherapy, the severity of neurotoxicity was lower than in the control group. The phase IIA clinical trial by Bao et al demonstrated that acupuncture intervention prevented progression to grade 3 CIPN in 26 of 27 patients (96%) with pre-existing grade 2 symptoms, while maintaining stable neurotoxicity scores (FACT/GOG-Ntx and NPS), suggesting significant efficacy in halting CIPN progression.[101]

Biological Agents

Emerging evidence has highlighted the therapeutic potential of biologics targeting neurotrophic, anti-inflammatory, and neuroprotective pathways for chemotherapy-induced peripheral neuropathy (CIPN). Notably, DS002, a monoclonal antibody against nerve growth factor (NGF) that effectively inhibits NGF-TrkA interaction, has become the first NGF-targeted agent demonstrating significant pain alleviation in CIPN animal models.[102] A corroborative study by Xie et al[103] revealed that prophylactic administration of ZR8 mAb, a monoclonal antibody targeting calcitonin gene-related peptide (CGRP), effectively mitigated cisplatin-induced mechanical allodynia and thermal hyperalgesia while attenuating neuroinflammatory responses. Although most of these interventions remain in early-phase trials, they collectively underscore the transformative potential of precision drug delivery systems and innovative combination strategies in optimizing therapeutic outcomes.

The treatment plans encompass both well-established therapies validated by clinical trials and potential approaches still in the theoretical verification stage. Table 4 systematically summarizes key data on commonly used clinical medications and therapeutic interventions, including their levels of evidence-based medical support and efficacy

Table 4 Therapies for Chemotherapy-Induced Peripheral Neuropathy (CIPN): Clinical Evidence Summary

Category	Treatment	Clinical Evidence	Side Effects
Neuroprotectants	Mecobalamin	Stimulates axonal regeneration and improves nerve conduction velocity.[69] Shown to alleviate metabolic dysfunction in neural tissues.	Gastrointestinal discomfort
Antidepressants	Duloxetine	ASCO guideline first-line recommendation for CIPN-related neuropathic pain.[104]	Dry mouth, constipation
	Amitriptyline	RCT (25 mg/day) showed no significant benefit vs placebo.[105]	Sedation
Opioids	Oxycodone	ASCO recommends as second/third-line for short-term refractory cases.[104]	Addiction risk
Metabolic Agents	Epalrestat	Confirmed efficacy for diabetic neuropathy in meta-analysis.[106]	Elevated liver enzymes
Topical Agents	Lidocaine	Direct analgesic effect with moderate-term benefits for allodynia.[85]	Local skin irritation
Mineral Supplements	Magnesium	NCCTG N04C7 trial: Reduced ≥grade 2 sensory neuropathy.[107]	Diarrhea
	Gabapentin	Not routinely recommended per ASCO (moderate evidence).[104]	Drowsiness
Physical Therapy	Cold Gloves	POLAR trial: 42% lower CIPN risk (HR=0.58) with good tolerability.[108]	Skin coldness
Acupuncture	Electroacupuncture	Phase IIA trial showed reduced CIPN severity during paclitaxel.[101]	Soreness at needle sites

(*Continued*)

Table 4 (Continued).

Category	Treatment	Clinical Evidence	Side Effects
NSAIDs	Celecoxib	Phase III data suggest benefit for chemotherapy-induced toxicities.[109]	Gastrointestinal irritation
Metal Complexes	Calmangafodipir	Phase II PLIANT study showed prevention of oxaliplatin neuropathy.[110]	Infusion site reactions

Notes: All therapies listed are supported by clinical evidence relevant to chemotherapy-induced peripheral neuropathy (CIPN), with efficacy varying by agent class and patient population. Recommendations for first-line vs second/third-line use are based on current guideline consensus (eg, ASCO) and strength of clinical evidence.
Abbreviations: CIPN, Chemotherapy-Induced Peripheral Neuropathy; ASCO, American Society of Clinical Oncology; RCT, Randomized Controlled Trial; HR, Hazard Ratio.

evaluations. This compilation is designed to provide clinicians with decision-making references for chemotherapy-induced peripheral neuropathy (CIPN) management and to expand treatment options for patients with nab-paclitaxel-induced peripheral neuropathy.

Summary

Paclitaxel is an antitumor drug that acts on microtubules, but the mechanism underlying its selective neurotoxicity remains unclear; however, the relatively high abundance of tubulin in neurons and the importance of an intact, functioning microtubular skeleton for nerve conduction can be partially explained. Tumor cells are a group of dividing cells at the proliferative stage, and tubulin condensation by taxol can hinder spindle formation and arrest tumor cells at the G2/M stage; and while nerve cells no longer possess cell-division abilities, the tubulin condensation of taxol can still affect the transmission of electrical signals in the axons by disturbing the formation of microtubules and lesioning peripheral nerve insulation. Neurotoxicity precipitated by antitumor drugs that act on microtubules are enhanced as the drug accumulates in the body, and it is higher in patients with existing neuropathic disease.[9] Neurotoxicity from this type of drug usually disappears after several months of withdrawal, but some patients manifest significant neurotoxic sequelae even years after withdrawal.

The key question to address is how to manage patients who receive potentially neurotoxic chemotherapy, and whether it is possible to prevent and/or mitigate symptoms of chemotherapy-induced neuropathy without limiting potentially life-saving chemotherapy. Patients should be instructed to report any signs of neuropathic pain, altered sensory perception, or any other CIPN symptoms. Furthermore, and particularly for high-risk patients, if a known neurotoxic chemotherapy is used, we recommend that a neurologic examination and electrophysiologic assessment be performed early in the treatment course and repeated as required by the specific clinical context. Doctors should watch the use of neurotoxic chemotherapies very carefully. It's best to lower the drug dose or mix it with other anticancer drugs that are less toxic to nerves. This can help cut down the chance or seriousness of CIPN.

In light of the aforementioned clinical management challenges, although progress has been made in mechanistic studies of chemotherapy-induced peripheral neuropathy (CIPN) and therapeutic strategies, several critical limitations persist in the field of Albumin-Paclitaxel -induced peripheral neuropathy. First, mechanistic understanding remains incomplete. While most studies have focused on microtubule destabilization, the molecular mechanisms underlying paclitaxel's specific targeting of sensory neurons remain elusive, particularly its interactions with ion channels (eg, TRPV1, Nav1.7) in dorsal root ganglia (DRG). Second, clinical translation faces bottlenecks. As previously discussed, although neurotrophic agents demonstrate significant efficacy in animal models, their clinical outcomes vary substantially, potentially due to inadequate blood-nerve barrier penetration or patient heterogeneity.

To address these challenges, future research should prioritize the following directions: (1) Development of multimodal therapeutic strategies, such as combining the aforementioned biologics with neuroprotective agents to enhance efficacy and reduce adverse effects through synergistic mechanisms; (2) Advancement of precision medicine applications by employing artificial intelligence models (as previously mentioned) to predict individualized CIPN risk and guide chemotherapy regimen adjustments; (3) Closer integration of clinical trials with contemporary basic research to further elucidate the regulatory

mechanisms of peripheral nerve injury repair, thereby achieving superior therapeutic outcomes. These research directions will not only address current limitations but also provide more effective solutions for clinical practice.

Abbreviations

nab- paclitaxel, albumin-bound paclitaxel; CIPN, chemotherapy-induced peripheral neuropathy; 3s approach, a new method combining compression therapy (using stockings and sleeves) and drug therapy; CTCAE, common terminology criteria for adverse events; BMI, body mass index; ER, estrogen receptor; Her 2, human epidermal growth factor receptor 2; PR, progesterone receptor; CI, confidence interval; CSAP, compound sensory nerve action potential; FACT-GOG-NTX-13, functional assessment of cancer therapy/gynecologic oncology group-neurotoxicity questionnaire; TNSC, total neuropathy score clinical version; OS, overall survival; PFS, progression-free survival; DCR, disease control rate; ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; BRCA1, breast/ovarian susceptibility gene 1; RT-PCR, Real-time Polymerase Chain Reaction; SYBR Green I, SYBR Green Nucleic Acid Gel Stains; BAP1, BRCA1 associated protein-1; PARP, Poly (ADP-ribose) polymerase; miRNA, MicroRNA; BRCT, breast cancer susceptibility gene C-terminal domain.

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