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Invited review

The paradox of paclitaxel neurotoxicity: Mechanisms and unanswered questions

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ABSTRACT

Paclitaxel is a microtubule-binding compound that is widely used as a chemotherapeutic in the treatment of common cancers, including breast and ovarian cancer. Paclitaxel binding along the length of microtubules stabilizes them and suppresses their dynamics, leading to mitotic arrest and apoptosis in dividing cells. Though they are not dividing cells, neurons are also susceptible to paclitaxel, and paclitaxel exposure results in axonal degeneration. Thus a frequent side effect of paclitaxel treatment in patients is peripheral neuropathy, which can necessitate dose reductions and have lasting symptoms. An understanding of the mechanisms underlying paclitaxel's neurotoxicity is important for development of therapeutics to prevent and alleviate the neuropathy. Here we will review approaches taken to investigate mechanisms of paclitaxel-induced neuropathy and evidence for potential mechanisms of the axonal degeneration downstream of or distinct from microtubule stabilization by paclitaxel.

This article is part of the Special Issue entitled 'The Synaptic Basis of Neurodegenerative Disorders'.

1. Introduction

1.1. Paclitaxel

Paclitaxel, often called by its brand name Taxol, is a microtubule-binding agent that is widely used as a chemotherapeutic in the treatment of breast, ovarian, and lung cancer. Microtubules are formed from heterodimers of α-tubulin and β-tubulin and paclitaxel binds to β-tubulin that has been incorporated into microtubules (Nogales et al., 1995). Normally, microtubules undergo depolymerization and repolymerization, a process known as dynamic instability (Mitchison and Kirschner, 1984). The current model for this process is that GTP-bound tubulin subunits are incorporated at the end of the microtubule, forming a cap. When the GTP is subsequently hydrolyzed, the tubulin subunit changes conformation, leading to destabilization of the microtubule lattice. A cap of GTP-tubulin will preserve the microtubule, but if GTP hydrolysis of the terminal subunits occurs, extensive depolymerization of the microtubule can occur during which the GDP-tubulin subunits will dissociate from the microtubule end (Nogales and Wang, 2006). Paclitaxel binding along the lumen of the microtubule stabilizes the microtubule lattice, thereby suppressing depolymerization and dynamic instability (Fig. 1). At higher concentrations than are needed to suppress dynamics, paclitaxel enhances the polymerization of microtubules (Derry et al., 1995; Dumontet and Jordan, 2010; Jordan et al., 1993). Paclitaxel is able to promote the polymerization of microtubules even in the absence of GTP, and these microtubules are resistant to depolymerization (Schiff et al., 1979; Schiff and Horwitz, 1981). The described molecular mechanism underlying paclitaxel's effects is through stabilization of the helical conformation of the M-loop of β-tubulin, which strengthens lateral contacts between tubulin subunits (Prota et al., 2013).

1.2. Paclitaxel-induced neuropathy

The dynamic instability of microtubules is crucial during mitosis because the polymerization dynamics of the mitotic spindle accomplish the proper alignment and segregation of chromosomes to daughter cells. Paclitaxel, by stabilizing microtubules, prevents the requisite dynamics and this leads to arrest of mitosis at G_2/M phase, and ultimately apoptosis (Jordan and Wilson, 2004). Therefore, paclitaxel is highly effective against proliferating cancer cells. It is widely used, both alone and in combination with other chemotherapeutic agents, in the treatment of many types of solid tumors, including breast, ovarian, lung, and head and neck cancers.

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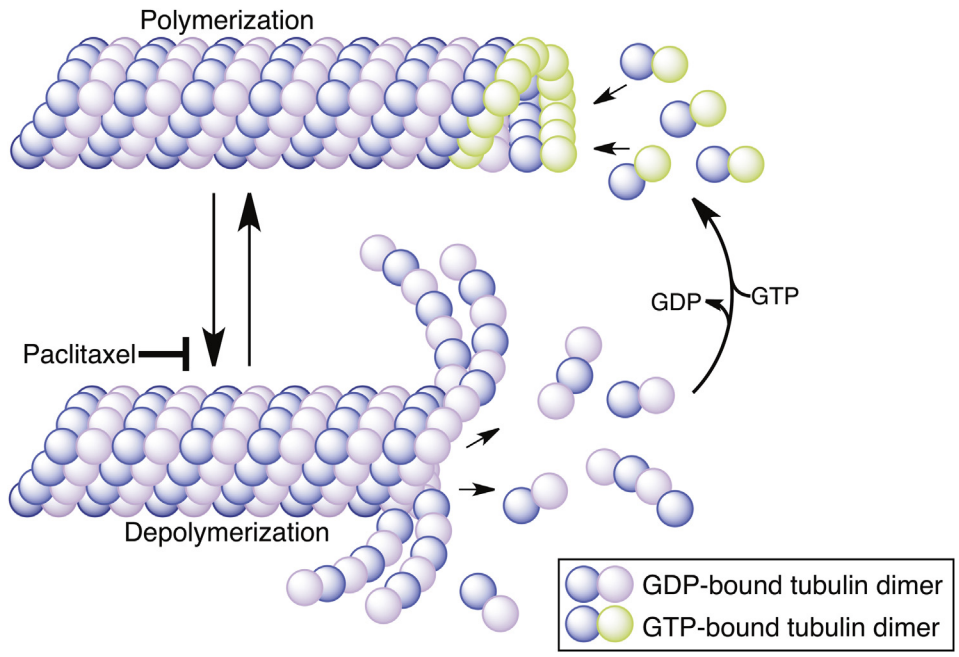

Fig. 1. Paclitaxel suppresses microtubule dynamic instability. GTP-bound tubulin dimers are incorporated into the growing end of the microtubules, and are thought to form a stabilizing cap of GTP-bound tubulin. Over time, GTP is hydrolyzed to GDP, which leads to a conformational change in tubulin dimers and destabilization of the microtubule lattice. Loss of the GTP-tubulin cap results in microtubule depolymerization. Nucleotide exchange primes released tubulin dimers for reincorporation into a microtubule. Paclitaxel prevents microtubule depolymerization.

Paradoxically, although they are not dividing cells, neurons are also susceptible to paclitaxel and this causes serious complications for its use as a therapeutic agent. As paclitaxel does not cross the blood–brain barrier, it specifically affects the peripheral system, and leads to a predominantly sensory axonal neuropathy (Park et al., 2011). The incidence and severity of the neuropathy increase with higher single and cumulative doses. Though the reported incidence varies depending on the study, up to 30% of patients experience severe symptoms at high cumulative doses (Carlson and Ocean, 2011). The neurological symptoms can reach such severity as to necessitate the cessation or reduction of treatment. Although symptoms usually resolve after discontinued treatment, they can persist for months or years, leading to a lower quality of life (Lee and Swain, 2006).

When a neurotoxic dose is reached, sensory symptoms begin in the hands and feet. This is reflective of a dying back neuropathy, in which the distal sensory axons degenerate (Argyriou et al., 2008). Peripheral nerve biopsy has revealed a pathology of axonal degeneration, secondary demyelination, and nerve fiber loss in cases of severe neuropathy (Sahenk et al., 1994). However, rat models have demonstrated that neuropathic symptoms can be present with degeneration of just the very distal intraepidermal fibers (Siau et al., 2006). Paclitaxel can affect all sensory modalities, with the large fibers being most affected (Quasthoff and Hartung, 2002; Dougherty et al., 2004). Primary symptoms in patients include numbness, pain, and tingling (Lee and Swain, 2006). The motor system is less frequently affected, with reports of mild symptoms at high paclitaxel doses, and effects on the autonomic system are rare (Freilich et al., 1996; Winer et al., 2004). Though studies have identified agents that protect against paclitaxel-induced axonal degeneration in cultured neurons (Melli et al., 2006, 2008; Rovini et al., 2010; Verstappen et al., 2004), and axonal degeneration and sensory symptoms in rodent models (Apfel et al., 1991; Boyle et al., 1999; Pisano et al., 2003; Wang et al., 2004), those that have been tested in clinical trials thus far have yielded mixed results, and there are currently no approved interventions.

A roadblock to identification of therapeutics for the paclitaxel-induced degeneration is the current lack of understanding of the underlying mechanism. If the degeneration is a direct consequence of stabilization of microtubules at the taxane-binding site, it may be impossible to prevent the neuropathy while preserving paclitaxel's chemotherapeutic effectiveness. But if there are mechanistic distinctions or downstream consequences of microtubule stabilization in neurons that are not important for mitotic arrest, there may be pharmacological opportunities to alleviate the neuropathy. This review will therefore examine the approaches that have been taken to address this question and will then discuss possible mechanisms of the neuropathy and the current state of evidence in support of those theories. How does the neuropathy relate to the known action of paclitaxel on microtubule stability? Do defects in microtubule-based axonal transport underlie the degeneration? How might stabilization of microtubules compromise the viability of the axon?

2. Studies of paclitaxel-induced degeneration

2.1. Experimental approaches

Studies in cultured dissociated neurons and explants have involved treating with paclitaxel and determining its effects on neurite length and morphology. Results have revealed that neurons in culture are also susceptible to paclitaxel, and the neurotoxicity is dose and time dependent as seen in the clinical setting (Letourneau and Ressler, 1984; Scuteri et al., 2006). After exposure to paclitaxel, axons fragment (Scuteri et al., 2006), develop swellings (Shemesh and Spira, 2010), or die back (Malgrange et al., 1994; Yang et al., 2009; Wang et al., 2002). When neurons are grown in a compartmentalized chamber that allows addition of paclitaxel to just the cell bodies or axons, axon length is reduced specifically when paclitaxel is added to the axons, suggesting that paclitaxel acts directly on the axon and induces axonal degeneration through local mechanisms (Yang et al., 2009). Studies in vitro delving further into