# Microtubule Poisons

Subjects: Oncology

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Microtubule poisons, as is the case with other antitumor drugs, routinely promote autophagy in tumor cells. However, the nature and function of the autophagy, in terms of whether it is cytoprotective, cytotoxic or nonprotective, cannot be predicted; this likely depends on both the type of drug studied as well as the tumor cell under investigation. The microtubule poisons continue to play a central role in the clinical treatment of both solid tumors or hematologic malignancies. However, tumor cells can develop resistance by a number of mechanisms such as altered microtubule binding and efflux via the multidrug resistance pump family of transporters.

Keywords: autophagy ; microtubule poison ; cytoprotective ; cytotoxic

## 1. Introduction

Microtubules are composed primarily of α- and β-tubulin subunits, each of which have a GTP-binding site. The GTP-binding site on the α-subunit is a non-exchangeable site (N site) in that the bound GTP cannot be hydrolyzed or replaced by GDP. In contrast, the GTP (exchangeable E) binding site on the β subunit can be hydrolyzed to GDP [1][2]. The α- and β-heterodimers assemble into linear “protofilaments” that further assemble into a regular helical lattice around a hollow core [3]. The formed microtubules have plus and minus ends, and the process is dynamic. The dynamics of tubulin addition and release are faster for β-tubulin subunits exposed at the plus end of microtubules, while slower for α-tubulin subunits exposed at the minus end. Adding tubulin heterodimers to microtubules activates the GTPase activity of β-tubulin, which locks β-tubulin in the microtubule into a GDP-bound state [4].

Microtubules are central components of cell division and produce spindle bodies to form new daughter cells in late cell division. In addition to α- and β-tubulin, γ-, δ-, ε-, ζ- and η-tubulin are also found in eukaryotes [5]. Among these, γ-tubulin is found primarily around the centrioles, promoting intracellular microtubule nucleation and controlling mitotic spindle replication. ε- and δ-tubulin are newly discovered members of the tubulin superfamily, which maintain the microtubule cytoskeleton structure. In addition to these functions, microtubules are one of the major components of the cytoskeleton, supporting and maintaining basic cellular morphology, forming cilia and flagella, assisting cell motility, and serving as “tracks” for intracellular nutrient transport [5][6].

The first natural products belonging to the category of microtubule poisons with potent antitumor properties for clinical use were the vinca alkaloids, vinblastine and vincristine [7], identified in 1960. Approximately 10 years later, paclitaxel was isolated from *Taxus brevifolia*. Taxol was not approved by the FDA until 30 years after it was initially isolated and identified; only three years later, the more sensitive formulation of docetaxel was developed [8][9]. These drugs are classified into two main categories, depending on whether they act as microtubule destabilizing agents (the vinca alkaloids) or microtubule stabilizing agents (the taxanes). Cell proliferation, migration, invasion, and material transport are all dependent on dynamic changes in microtubule polymerization and depolymerization [4][10][11].

## 2. Direct Involvement of Microtubules in Autophagy

When microtubule-associated protein 1A/1B-light chain 3 (MAP1LC3, LC3) was identified as a key factor in the induction of autophagy, the Yoshimori laboratory had proposed the idea that microtubules might be involved in the progression of autophagy by affecting the efficient transport of autophagosomes to mammalian cells [12]. It was later confirmed that microtubules participate in the fusion of autophagosomes with lysosomes and in the formation of late autophagosomes [13][14].

The importance of microtubules in autophagic flux has long been recognized, and their role in autophagy initiation, trafficking, and lysosomal fusion has been continuously revealed in the last two decades. In addition to LC3, other autophagy-related proteins such as ULK1, Beclin-1, WIP1, ATG5, and ATG12 that are involved in autophagosome formation were found to be associated with microtubules as well [15][16][17]. Dynamic changes in microtubule and post-

translational modifications of microtubule play an important role in regulating starvation-induced autophagy, as microtubule acetylation occurs prior to autophagosome formation in response to nutrient deficiency. Acetylation modification signals kinesin recruitment to microtubules, followed by JNK activation and Beclin-1 release from the Beclin-1-Bcl-2 complex to initiate autophagy [15].

AMBRA1 is a key factor in the regulation of autophagy in vertebrates. AMBRA1 promotes the interaction of Beclin-1 with its target lipid kinase, VPS34, which mediates autophagosome nucleation [18]. Moreover, AMBRA1 serves as a direct regulatory link between ULK1 and Beclin-1-VPS34, which is required for the localization and activity of the intracellular core complex. Once the autophagosome is formed, it moves along the microtubule in both directions (minus-end and plus-end) via kinesin motor complexes, accumulating at the microtubule-organizing center, and eventually moving towards the lysosome [13][14][19]. Their centripetal movement is dependent on the motor protein dynein and is important for their fusion with lysosomes. In addition to the function of microtubules mediating autophagosome transport, there is a strict regulatory relationship between cytoskeletal dynamics and autophagosome formation [17].

The effect of microtubules on the fusion of autophagosomes with lysosomes is controversial. One view is that microtubule dynamics does not affect the fusion of autophagosomes with lysosomes and that this fusion can occur in the presence of microtubule poisons [20][21]. However, by combining real-time observation and microinjection techniques, other investigators proposed that after formation, autophagosomes utilize a dynein-microtubule system to rapidly move toward lysosomes located near the centrosome [14]. When cells are starved for glucose, the cyclin-dependent kinase inhibitor p27Kip1 (p27) promotes autophagy by maintaining elevated microtubule acetylation via an ATAT1-dependent mechanism to promote autophagosome transport along microtubule trails [22].

In addition to their classification into the two main categories, namely microtubule destabilizing agents and microtubule stabilizing agents, microtubule poisons are then subdivided into the following categories according to their specific binding domains to microtubule proteins (**Figure 1**): colchicine site, vinca alkaloid site, taxane site, laulimalide site and epothilone site. Analysis of autophagy induced by different microtubule poisons in tumor therapy is based on these subcategories.

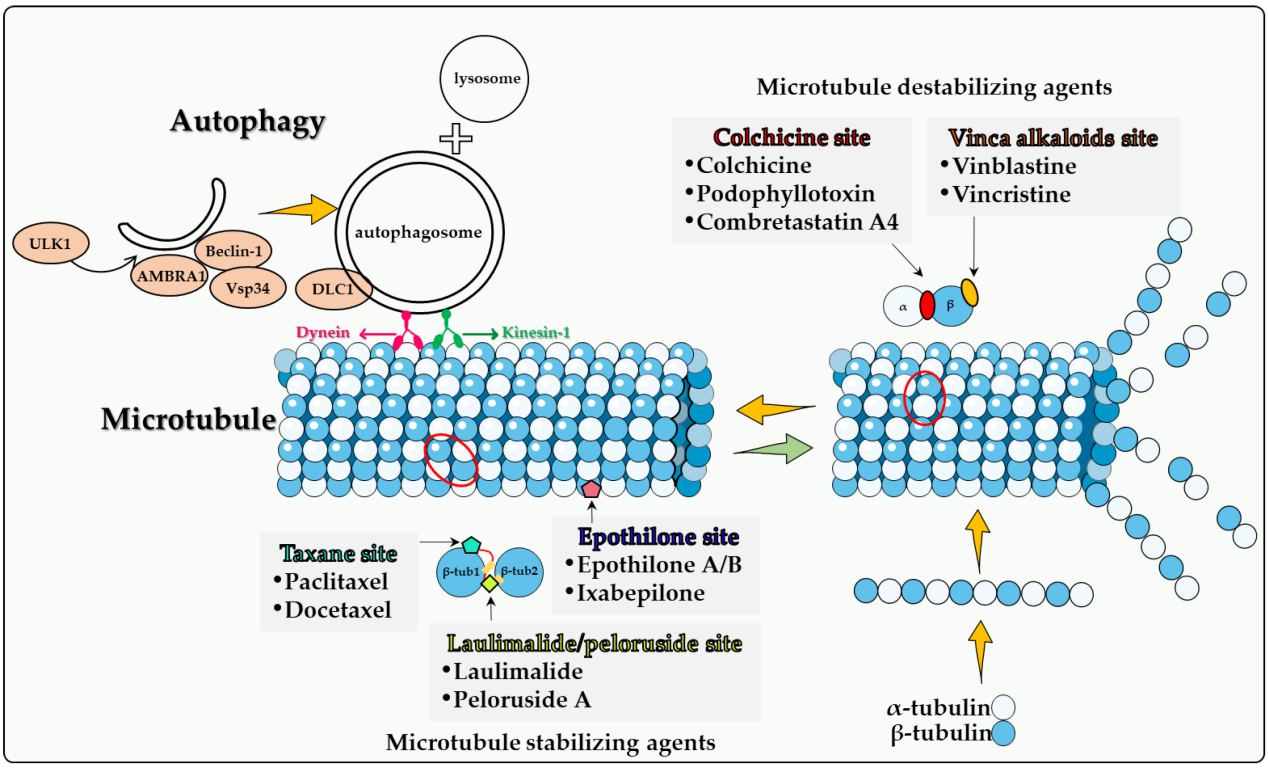


**Figure 1. The binding sites of microtubule poisons and autophagy.** Kinesin-1 and dynein are microtubule motors that transport intracellular cargos. Once formed, the autophagosome travels along the microtubule via kinesin motor complexes, accumulating at the microtubule-organizing center, and eventually moving towards the lysosome. This centripetal movement is dependent on the motor protein dynein and is required for their fusion with lysosomes. Microtubule poisons are classified into two main categories, depending on whether they act as microtubule destabilizing agents or microtubule stabilizing agents. Microtubule destabilizing agents: Colchicine, Podophyllotoxins and Combretastatin A-4 target the colchicine site between α- and β-tubulin subunits (red dot); Vinca alkaloids bind to the β-tubulin subunit of the α/β-tubulin heterodimer (yellow dot). Microtubule stabilizing agents: Paclitaxel and Docetaxel target the Taxane site, binding to the β-tubulin subunit (green pentagon). Laulimalide and Peloruside A binding involves the

bridging of two adjacent tubulin dimers (β-tubulin1 and β-tubulin2) across protofilaments in microtubules (light green squares). Epothilone sites and Taxane sites are different. Among the five oxygen-containing polar groups constituting the macrocycle of epothilone, only C7-OH is located near the similar C7-OH moiety of paclitaxel, and the polymerization activity of epothilone B is 2 to 10 times higher than that of paclitaxel (pink pentagon).

### 2.1. Colchicine Site

*Colchicine.* Colchicine, an alkaloid isolated from plants belonging to the genus *Colchicum* (*Autumn crocus*), is a classical antimitotic compounds, but is not actually used in cancer therapeutics due to its high degree of toxicity [23]. Colchicine blocks mitotic cells in metaphase through the formation of poorly reversible tubulin–colchicine complexes. In addition, colchicine binds to microtubule ends, thereby preventing elongation [23].

Although colchicine has potent antitumor properties that are attributed to the irreversible binding with tubulin causing cell cycle inhibition and the induction of apoptosis, colchicine lacks selectivity against tumor cells. This limitation has led to the development of colchicine derivatives as well as colchicinoid prodrugs with less toxicity and more specific targeting to tumor cells [24].

JG-03-14, a substituted pyrrole colchicine mimetic that binds to the colchicine site of tubulin, induced a significant reduction in the viability of MCF-7 and MDA-MB-231 cells [25]. Importantly, JG-03-14 was able to induce autophagy in up to 70% of the MCF-7 cell population by the third day of treatment with minimal apoptosis (as evidenced by the TUNEL assay). Conversely, JG-03-14 induced a significant amount of apoptosis by the third day of treatment in the MDA-MB231 cell line, but also demonstrated a significant degree of autophagy, based on acridine orange staining [25]. These findings suggest that JG-03-14 may have induced autophagic cell death in these breast tumor cell lines, although the precise function of the autophagy was not directly assessed.

*Combretastatin A-4*. Combretastatins represent a large family of bioactive stilbenes, dihydrostilbenes, phenanthrenes and macrocyclic lactones named Combretastatins A, B, C, and D, respectively [26]. Combretastatins are isolated from *Combretum caffrumtree* and show favorable anticancer activities. A well-studied member of this drug family is Combretastatin A-4 (CA-4), a tubulin-depolymerizing agent that binds at the colchicine binding site on the β-tubulin subunit of tubulin, resulting in depolymerization and destabilization of tubulin polymers of the cytoskeleton, causing an increase in vasculature permeability and disruption of the tumor blood flow [26][27][28][29].

Combretastatin A4 phosphate is a prodrug for CA-4 that has shown a potential anti-cancer effect in Phase I clinical trials [30]. Hoang et al. [31] showed that the anti-tumor effect of CA-4 phosphate is enhanced in autophagy-defective PC3 prostate cancer xenografts (developed with retrovirally transducing PC-3 cells with ATG4BC74A, an inactive and dominant-negative mutant of the autophagy related gene atg4B) compared with controls. Significant central necrosis as well as a higher number of senescent cells were evident in autophagy-defective PC3 xenografts both 24 h and 1 week following CA4P treatment, indicating the possible role of autophagy inhibition (i.e., cytoprotective autophagy) in enhancing the antitumor effects of CA4 phosphate via lowering the threshold of peripheral tumor cells to tolerate the CA4 phosphate-induced metabolic stress [31][32].

Taken together, these findings suggest that combretastatin-mediated autophagy is largely cytoprotective but can also be dependent on both the cancer type as well as the specific cell line studied.

### 2.2. Vinca Alkaloid Site

Vinca alkaloids are a class of organic compounds that were isolated from the leaves of the Madagascar periwinkle plant, *Catharanthus roseus*. Five distinct vinca compounds with significant antineoplastic activities have been identified, specifically vinblastine, vincristine, vindesine, vinorelbine, and vinflunine. Vinblastine and vincristine continue to be two of the most commonly used anticancer agents. These drugs are structurally related except that vincristine contains an aldehydic functional group attached to the nitrogen of the indole moiety whereas vinblastine contains a methyl group. This minor difference in structure results in significant differences in both the antineoplastic activities and the toxicity between the two agents [33]. Vinblastine has been utilized in the clinical treatment of leukemia, non-Hodgkin’s and Hodgkin’s disease, breast cancer, testicular carcinoma, and small-cell lung cancer. Vincristine have been used for many years in the treatment of malignancies including acute lymphoblastic leukemia, B-cell lymphoma, metastatic melanoma, and Wilms’ tumor [34].

Vinca alkaloids bind the vinca binding site on microtubules causing microtubule interruption and dissociation [35]. Vinca alkaloids tend to demonstrate cell cycle specificity for the M-phase [36]. At low concentrations, these drugs decrease the

rates of both growth and shortening at the microtubule assembly end, blocking mitosis, with the cells eventually undergoing apoptosis [37]. At high concentrations, vinca alkaloids cause microtubule depolymerization and the destruction of mitotic spindles. The dividing tumor cells show condensed chromosomes and appear to be blocked in mitosis [38]. Furthermore, vinca alkaloids exhibit antiangiogenic and antivascular activities, inducing potent vascular disruption, and ultimately leading to tumor necrosis [39][40].

The function of autophagy is likely to vary between different experimental tumor models. In some cases, vincristine cytotoxicity may be hindered by the cytoprotective form of autophagy, while in other cases cytotoxic autophagy is expressed.

### 2.3. Taxane Site

*Paclitaxel.* Paclitaxel, an antimitotic agent originally extracted from the bark of the Pacific yew tree, was identified and developed by Dr. Susan Band Horwitz in 1979 [41]. Paclitaxel binds to the β-tubulin subunit and forms stable and nonfunctional microtubules, thereby blocking cancer cell growth by interrupting cell division at the metaphase/anaphase transition, resulting in cell death [42][43]. This is a mechanism quite different from that of vincristine and vinblastine, which cause the disassembly of microtubules. Since its approval by the FDA, Taxol, a semisynthetic form of paclitaxel, has expanded treatment options for patients with breast [44] and ovarian cancers [45]. Non-small cell lung cancer, pancreatic cancer, and AIDS-related Kaposi sarcoma are all sensitive to Taxol as well [46][47].

The autophagy caused by paclitaxel in different types of tumor cells appears to be drastically different. Zou et al. found that paclitaxel *cannot* induce autophagy in SKBr3 and MDA-MB-231 breast cancer cells, unless ARHI (DIRAS3) is re-expressed in the cells [48]. Veldhoen et al. found that low concentrations of paclitaxel inhibited autophagy. It was suggested that paclitaxel-induced mitotic arrest leads to decreased autophagic flux through phosphorylation and inhibition of Vps34 and subsequently results in aberrant autophagosome trafficking and localization, which in turn inhibits autophagosome degradation. By detecting autophagosome formation of GFP-LC3 fluorescence in single cells and cell death using flow cytometry, these investigators demonstrated that 3-MA, siRNA ATG7, or siRNA VPS34 reduced paclitaxel-induced apoptosis, suggesting that the blocked autophagy still plays a key role in paclitaxel-induced cell death [49]. These studies appear to support a direct role of (cytotoxic) autophagy in paclitaxel-induced cell death.

### 2.4. Epothilone Site

*Epothilone A and epothilone B*. Epothilones are a type of natural cytotoxic compound belonging to 16-member natural macrolides. Thus far, six types of epothilone and derivatives have been reported. Epothilone A and B were first isolated from myxobacterium *Sorangium cellulosum*, and the efficiency of epothilone B was shown to be higher than that of epothilone A [50]. Similar to paclitaxel, epothilone also exerts its antitumor activity by stabilizing cell microtubules, but the binding sites of epothilone and paclitaxel are different. Among the five oxygen-containing polar groups constituting the macrocycle of epothilone, only C7-OH is located near the similar C7-OH part of paclitaxel, and the polymerization activity of epothilone B is 2 to 10 times higher than that of paclitaxel [51]. In addition, epothilone is less susceptible to multidrug resistance pump-mediated efflux compared to paclitaxel, and the expression of MDR is not altered in epothilone-resistant cell lines, implying a wider choice for chemo-resistant patients [52][53].

### 2.5. Laulimalide/Peloruside Site

*Laulimalide and Peloruside A*. Laulimalide is a potent microtubule stabilizer that was originally isolated from the sponge *Cacospongia mycofijiensis* [54]. Peloruside A was isolated from the New Zealand marine sponge Mycale hentscheli in 2000 [55]. Researchers found that peloruside A and laulimalide compete for the same or overlapping binding sites, not taxane site but the M-loop of β1 and loop H1−B2 of β2 [56][57][58]. In contrast to paclitaxel, peloruside A and laulimalide are not substrates for the multidrug resistance P-glycoprotein efflux pump and are not affected of β-tubulin mutations in the taxane binding site [56]. These properties indicate that laulimalide and peloruside A have the potential to treat paclitaxel resistant tumors, but no clinical trials are currently in progress due to a limited drug supply, unstable drug structure [59] and the lack of antitumor activity studies in vivo.

## 3. Summary

Although many new cancer treatments have been developed in recent years, such as targeted therapy and immunotherapy, microtubule poisons remain a critical class of first-line chemotherapeutic agents. However, the relationship(s) between microtubule poisons and autophagy are exceedingly complex. This is likely due to a number of factors including that (a) microtubules play a direct role in the autophagic process; (b) the different microtubule poisons do

not all act at the identical microtubule binding sites, as indicated in **Figure 1**; (c) autophagy cannot have only one (cytoprotective) function, but (at least) three others, termed cytotoxic, cytostatic and nonprotective. Although the cytoprotective function is often clearly induced, both the cytotoxic and nonprotective function have also been identified in response to these agents. This may be dependent upon the chemical structure of the drug as well as the experimental cell line being utilized. final and critical issue is that the literature evaluating the role of autophagy in response to microtubule poisons in tumor cells has generally relied on pharmacologic autophagy inhibitors such as CQ (or HCQ) and 3-MA drugs, which are not exclusively autophagy inhibitors [60]. In the absence of studies utilizing genetic autophagy inhibition, inferences related to the nature of the autophagy are not sufficiently well supported to be conclusive.

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