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Microtubule-Binding Proteins as Promising Biomarkers of Paclitaxel Sensitivity in Cancer Chemotherapy

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Abstract

Microtubules, tirelessly animated and highly dynamic structures, are vital for most cellular processes and their intricacies are still being revealed even after a century since their discovery. The importance of microtubules as chemotherapeutic targets cannot be overstated, and their clinical role is unlikely to abate in the near future. Indeed, improved understanding of microtubule biology could herald a new epoch of anticancer drug design by permitting fine-tuning of microtubule-targeting agents, the clinical utility of which is presently often limited by primary or acquired resistance. Paclitaxel, one such agent belonging to the taxane family, has proven a resoundingly successful treatment for many cancer patients; however, for too many others with paclitaxel-refractory tumors, the drug has offered nothing but side effects. Accumulating evidence suggests that microtubule-binding proteins (MBPs) can regulate paclitaxel sensitivity in a wide range of cancer types. Improved understanding of how these proteins can be assayed to predict treatment responses or manipulated pharmacologically to improve clinical outcomes could transform modern chemotherapy and is urgently awaited.

Keywords

cancer chemotherapy; paclitaxel sensitivity; microtubule-binding protein; mitotic arrest; apoptosis

1. INTRODUCTION

One of the greatest mysteries that baffled early cell biologists was the origin of the force that moves chromosomes during mitosis. Around 1880, it was hypothesized by Klein and van Beneden that the “fibrillae” of the mitotic spindle (or the achromatic figure, as it was called) were contractile, like myocytes, and thus could pull the chromosomes toward fixed spindle poles.¹ Others did not even believe the fibrillae existed, speculating that they were merely artifacts of fixation. However, in the late 1940s, Inoué ultimately visualized these structures in living cells using a polarization microscope that he assembled by tying a modified Zeiss

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CONFLICT OF INTEREST

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microscope to a discarded machine gun base with twine.^{2, 3} Around 15 years thereafter, gazing upon electron micrographs of these elusive tubular structures, Slautterback aptly denominated them “microtubules.”⁴ Since then, microtubules have been intensively researched, and the forces intrinsic and extrinsic to them that direct their behavior, such as their tug-of-war with chromosomes,⁵ have been characterized in extensive detail. These long, hollow polymers of α/β -tubulin heterodimers participate in a multiplicity of eukaryotic cellular activities, including cell shaping, division, motility, signaling, and intracellular transport.

Although microtubules are not contractile per se, as originally hypothesized, they also are not static, but rather constantly growing and shrinking. This perpetual restlessness, termed dynamic instability, underlies microtubule function. Dynamic instability permits microtubules to expeditiously reorganize, such as during the swift transition between interphase and mitosis, when the interphase array must be refashioned into the fusiform mitotic spindle apparatus. It also allows microtubules to probe the intracellular milieu for their targets, such as kinetochores, and to oscillate between pushing and pulling, central to aligning chromosomes along the metaphase plate for equipartitioning to daughter cells.⁶ Given that dynamic instability is crucial for microtubules to carry out their multifarious roles in the cell, it comes as no surprise that this nonequilibrium behavior is tightly regulated by a variety of microtubule-binding proteins (MBPs),⁷ several of which we will succinctly describe in this paper.

Throughout the history of cancer research, few chemotherapeutic targets have rivaled microtubules in their effectiveness. Microtubule-targeting agents, such as taxanes and *Vinca* alkaloids, are treatments for a host of malignancies.⁸ Paclitaxel, a member of the taxane family, was first isolated from the bark of the Pacific yew. This complex diterpene has been hailed as one of the greatest success stories of all the microtubule-targeting drugs. Since it secured FDA approval in 1992 for treatment-refractory ovarian cancer, paclitaxel has proven efficacious in other solid tumors, including breast and non-small-cell lung carcinomas and Kaposi sarcoma. In addition, an albumin-stabilized nanoparticle formulation is used to treat metastatic pancreatic cancer. Despite paclitaxel's many triumphs, however, the variable sensitivity of patients to this drug curtails its clinical utility and poses a formidable hurdle to oncologists. The precise mechanisms underlying paclitaxel sensitivity remain largely unknown, in spite of decades of effort worldwide to decipher this molecular riddle. Emerging evidence shows that paclitaxel interacts with the mitochondrial antiapoptotic protein Bcl-2 by mimicking the Nur77 binding motif,⁹ which results in the initiation of apoptosis and thus makes the mitochondrial network a critical regulator of paclitaxel sensitivity.^{10–14} Herein, because the primary action of paclitaxel in the microtubule network occurs through interaction with β -tubulin, we present the mechanisms implicating MBPs that have thus far been elucidated (Table I).

2. MBPS: A SUBSET OF MOLECULES THAT MODULATES PACLITAXEL SENSITIVITY

It has been robustly demonstrated that paclitaxel binds to a unique pocket on β -tubulin at the lateral interface between adjacent protofilaments (Fig. 1A), and binding can induce a

conformational change in tubulin from an M-loop to a short helix structure.¹⁵ This alteration is believed to result in enhanced microtubule assembly and stability, thereby resulting in mitotic arrest and eventually apoptotic cell death. Cellular factors that alter the paclitaxel–tubulin interaction have the potential to affect paclitaxel sensitivity. MBPs, a diverse group consisting of canonical MBPs, microtubule-destabilizing proteins, microtubule plus end-tracking proteins, and noncanonical MBPs, have been found in preclinical and clinical studies to modulate the sensitivity of cancer cells to paclitaxel through their impact on microtubule dynamics (Fig. 1B). To fine-tune microtubule behavior, so essential to a wide range of cellular processes, the activity of these proteins must be precisely orchestrated, most often through posttranslational modifications, such as phosphorylation and acetylation; otherwise, pathologies, such as tauopathies, may occur. Furthermore, cancer aggressiveness and resistance to paclitaxel are attributed to altered expression levels of MBPs,^{16–18} underscoring the critical role they play in carcinogenesis and the importance of understanding their mechanisms of action.

Genomic and proteomic profiling of novel MBPs may offer a unique opportunity to select cancer patients for paclitaxel-based therapy. For example, microtubule-associated protein (MAP) 7 domain-containing protein 3, a newly identified MBP,^{19, 20} plays an integral role in breast cancer growth and metastasis.²¹ The familial cylindromatosis tumor suppressor CYLD, which modulates microtubule dynamics, cell migration, cell division, angiogenesis, and ciliogenesis, is also involved in cancer development and progression.^{22–27} In addition, CYLD has recently been demonstrated to promote noscapine binding to microtubules and stimulates its activity to induce mitotic arrest and apoptosis in acute lymphoblastic leukemia.²⁸ Characterization of the synergistic effects of these novel MBPs with paclitaxel merits further investigation. Ultimately, these MBPs could be targeted to improve paclitaxel sensitivity, which might allow reductions in the dose of paclitaxel and thereby minimize toxicity.

3. CANONICAL MBPS FILL THE CANONS ABOUT PACLITAXEL RESISTANCE

Canonical MBPs are structural MAPs, such as MAP2 and tau. They bind along the side of microtubules and, in most cases, stabilize microtubules by promoting the polymerization and formation of microtubule bundles (Fig. 1B). The MAP–microtubule interaction is usually orchestrated by MAP phosphorylation. Upon phosphorylation by microtubule affinity regulating kinase, MAPs detach from microtubules, leading to microtubule depolymerization.²⁹ MAPs are frequently deregulated in pathological conditions. A notable example is abnormally hyper-phosphorylated tau found in the paired helical filaments, one of the hallmarks of Alzheimer’s disease.³⁰

There is mounting evidence that phosphorylation of tau diminishes its microtubule assembly-promoting activity.^{31–33} However, the effect of tau phosphorylation on microtubule dynamics is less relevant to the subject of cancer cell sensitivity to paclitaxel than expression levels, which correlate closely with paclitaxel sensitivity in breast cancer.^{34, 35} Knockdown of tau expression in breast cancer with siRNAs augments cancer cell sensitivity to paclitaxel.³⁵ In general, tau is thought to bind the outside of the

microtubule, while the paclitaxel binding pocket is on the luminal side. In addition, tau has been reported to induce cooperative paclitaxel binding to microtubules,³⁶ and binding of paclitaxel to microtubules assembled in the presence of tau is diminished.^{34, 37} As tau expression levels are inversely correlated with breast cancer sensitivity to paclitaxel, low tau expression might be a valuable marker of a tumor's sensitivity to paclitaxel. Moreover, combining paclitaxel with agents that suppress tau expression might produce synergistic effects and thereby improve outcomes for patients with breast cancer. Panax notoginsenoside Rb1 (PNRb1), an effective agent for Alzheimer's disease treatment, was found to curtail the expression of tau in Alzheimer's disease models.³⁸ However, whether the effect of PNRb1 on tau expression could benefit paclitaxel-based chemotherapy remains unclear. It is important to investigate in the future whether paclitaxel combined with PNRb1 would have synergistic effects on cancer cells.

Although both tau and MAP2 have the ability to stabilize microtubules, they modulate cancer sensitivity to paclitaxel via distinct mechanisms. In contrast to tau, MAP2 promotes paclitaxel sensitivity in breast cancer cell lines.³⁹ Gene expression analyses have revealed that the expression of MAP2 is significantly increased in breast cancer patients who experience a pathologic complete response to neoadjuvant paclitaxel with radiation, suggesting that patients with high MAP2 expression are likely to benefit from paclitaxel treatment. Exploiting pharmacologic agents that elevate MAP2 expression is thus considered an attractive approach to enhance paclitaxel sensitivity. It is tempting to hypothesize that regimens combining paclitaxel with agonists of the Notch pathway, which can upregulate MAP2 expression,⁴⁰ would be particularly effective as a chemotherapeutic strategy.

4. REVVING UP THE ARENA OF PACLITAXEL RESISTANCE: MICROTUBULE-DESTABILIZING PROTEINS AS PROMISING BIOMARKERS AND THERAPEUTIC TARGETS

Microtubule-destabilizing proteins, of which stathmin is the best characterized, can increase the frequency of microtubule catastrophe (the transition from growth to shrinkage) and inhibit microtubule assembly. Stathmin acts as an important regulator of microtubule dynamic instability by sequestering free α/β -tubulin heterodimers into a ternary complex, thereby resulting in microtubule depolymerization⁴¹ (Fig. 1B). The microtubule-destabilizing activity of stathmin is controlled by phosphorylation in different cell cycle phases.⁴² Phosphorylation of stathmin attenuates its tubulin-sequestering activity,⁴³ allowing for entry into mitosis by promoting the formation of spindle microtubules. The action of stathmin phosphorylation on microtubule dynamics, however, has little influence on paclitaxel sensitivity, whereas elevated expression of stathmin seems to play a predominant role in cancer susceptibility to paclitaxel treatment.⁴⁴

Stathmin is highly expressed in a variety of human cancers, and inhibition of stathmin expression has synergistic anticancer and antiangiogenic effects with paclitaxel treatment through the stabilization of microtubules.⁴⁵ Overexpression of stathmin in breast cancer cells significantly attenuates the binding of paclitaxel to microtubules and arrests cells at the G2/M checkpoint, thus leading to paclitaxel resistance.⁴⁶ Furthermore, high stathmin

expression predicts poor prognosis in ovarian cancer patients treated with paclitaxel and platinum, conceivably because stathmin interferes with the effects of paclitaxel on microtubule assembly and stability.⁴⁷ These studies suggest that low stathmin expression may predict sensitivity to paclitaxel. Other studies demonstrate that suppression of stathmin expression sensitizes cancer cells to paclitaxel and inhibits their proliferation in a synergistic fashion.^{48–50} In addition, preclinical and clinical investigations indicate that stathmin reliably predicts the response of endometrial cancers to paclitaxel therapy.⁵¹ Collectively, these findings suggest that stathmin could be a therapeutic target and also serve as a promising biomarker for sensitivity to paclitaxel-based therapy in various types of cancer.

5. MICROTUBULE PLUS END-TRACKING PROTEINS COULD BE TRACKED TO PREDICT RESPONSE AND ATTACKED TO IMPROVE IT

Microtubule plus ends, which alternate between periods of growth and shrinkage, provide a key platform for coupling microtubules to organelles and cellular structures, such as the cell cortex, chromosomes, and the actin cytoskeleton.^{52, 53} Microtubule plus end-tracking proteins, also known as +TIPs, accumulate at the plus ends of growing microtubules and thereby modulate microtubule dynamics and functions (Fig. 1B). Members of the end-binding protein (EB) family are master regulators of the dynamic +TIPs network. EB proteins bind directly to the growing microtubule plus ends via their N-terminal calponin homology domain, whereas their C-terminus is responsible for the interaction with a diversity of other +TIPs. EB1 is able to recruit many other +TIPs to the microtubule ends; for example, adenomatous polyposis coli (APC) and cytoplasmic linker protein 170 (CLIP-170) localize to microtubule plus ends in an EB1-dependent manner.⁵⁴ EB1 is also known to coordinate with many other MBPs to regulate microtubule dynamics.^{55, 56} It is well established that EB1 and EB3, but not EB2, stimulate microtubule assembly and stabilization.⁵⁷ Consistent with their roles in regulating microtubule dynamics, EB1 and EB3 sensitize microtubules to microtubule-targeting agents by modulation of microtubule catastrophe.⁵⁸

A recent study revealed that the expression of EB1 correlates with clinical response to paclitaxel-based chemotherapy in breast cancer patients.⁵⁹ In vitro studies have shown that EB1 regulates paclitaxel-induced mitotic arrest and apoptosis via its influence on microtubule dynamics. Similarly, EB1 regulates paclitaxel sensitivity by modulating the paclitaxel-microtubule association, in that way affecting microtubule assembly and stabilization. Other studies have also substantiated the critical role of EB1 in regulating cancer cell sensitivity to paclitaxel, which it accomplishes by impacting the ability of paclitaxel to bind to growing microtubule plus ends.^{10, 60} In addition, EB1 has been reported to modulate the activity of the mitotic kinase Aurora B,^{61, 62} which may impact the activity of paclitaxel to cause mitotic arrest. These findings suggest that EB1 is a vital regulator of paclitaxel sensitivity in human cancers.

CLIP-170 is another member of the +TIPs family that has been pinpointed as a mediator of breast cancer cell sensitivity to paclitaxel. The expression of CLIP-170 correlates with paclitaxel sensitivity in breast cancer cell lines and the pathological response of tumors to paclitaxel-based chemotherapy.⁶³ Similar to EB1, CLIP-170 affects the interaction of

paclitaxel with microtubules, thus altering the ability of paclitaxel to promote microtubule assembly and contributing to cell-cycle arrest and apoptosis.

Mitotic centromere-associated kinesin (MCAK), a member of the kinesin family that stimulates microtubule catastrophe, has recently been implicated in paclitaxel resistance. Specifically, MCAK promotes paclitaxel resistance by encouraging microtubule detachment from centrosomes, although the precise mechanism remains elusive.^{64, 65} Interestingly, MCAK is directed to microtubule ends via its interaction with EB1.^{54, 66} Given that EB1 is a loading factor for many other +TIPs, we propose that EB1 may coordinate with other +TIPs to regulate breast cancer sensitivity to paclitaxel, in addition to direct modulation of paclitaxel-microtubule binding.

6. OUTSIDE THE ORDINARY: NONCANONICAL MBPS AS HARBINGERS OF TREATMENT RESPONSE

Noncanonical MBPs that regulate paclitaxel sensitivity consist primarily of proteins involved in the regulation of cell proliferation and survival, such as parkin and survivin. Parkin is an E3 ubiquitin ligase associated with Parkinson's disease that binds strongly to tubulin to facilitate the degradation of misfolded proteins.⁶⁷ In addition to its role in neurodegenerative disorders, parkin is a tumor suppressor protein that negatively regulates the growth of cancer cells.^{68, 69} In breast cancer, higher parkin expression is associated with a better response to paclitaxel-containing chemotherapy.⁷⁰ Mechanistically, parkin binds to the outer surface of microtubules and promotes the paclitaxel-microtubule interaction, leading to an increase in paclitaxel-induced microtubule assembly and stabilization.⁷⁰ Therefore, paclitaxel-based therapy might be more beneficial to breast cancer patients with higher parkin levels.

Survivin, as a member of the inhibitor of apoptosis family, is upregulated in almost all types of cancer.⁷¹ The localization of survivin to the mitotic spindle during mitosis occurs by virtue of its interaction with microtubules. Inhibition of the survivin-microtubule interaction promotes apoptosis.⁷² Survivin regulates the therapeutic effect of microtubule-targeting agents by contributing to microtubule stabilization.⁷³ For instance, upregulation of survivin mediates resistance to paclitaxel in head and neck cancer.⁷⁴ In addition, survivin increases paclitaxel resistance in ErbB2-overexpressing breast cancer cells by hastening mitotic exit that may help the cells to overcome paclitaxel-mediated mitotic arrest and thereby survive.⁷⁵ Thus, inhibition of survivin expression would likely be an effective strategy to increase paclitaxel sensitivity in certain cancer types.

7. PERSPECTIVE: TAPPING INTO PACLITAXEL'S POTENTIAL WITH PRECISION MEDICINE

The heterogeneous nature of cancer presents a daunting challenge to the design of broadly effective treatments. Ideally, optimal therapy would be selected based on the presence of molecular markers that predict tumor susceptibility to chemotherapeutic agents in an individual patient's tumor. At present, primary and acquired resistance to paclitaxel are common and markedly limit the drug's clinical utility. Tests that could reliably predict a

patient's response to paclitaxel would revolutionize cancer treatment by sparing patients the often devastating side effects of this drug if it would offer little benefit to them. Moreover, deeper understanding of the role of MBPs in regulating the paclitaxel–microtubule interaction could guide the rational design of more refined regimens with higher selectivity and efficacy. As we have catalogued, several MBPs possess the ability to modulate paclitaxel sensitivity by impacting microtubule structure. Altering the expression of these proteins or their posttranslational modifications could augment paclitaxel's effects on microtubule dynamics and lead to a synergistic inhibition of cancer cell proliferation (Fig. 1C). Therefore, these proteins not only hold the potential to serve as molecular markers to predict response to paclitaxel, but also could be manipulated to induce paclitaxel sensitivity, making them especially promising subjects for investigation. In addition, other tumor biomarkers alone or together with these MBPs could also benefit those patients who are administered a combination of paclitaxel and other chemotherapeutic agents or targeted therapies.^{76–78}

As yet, large-scale genomic and proteomic profiling of reliable markers to distinguish patients with differential sensitivity to paclitaxel have been undertaken, and a number of potential biomarkers have been identified.^{79–83} Further validation of these markers in clinical trials is thus urgently needed. Such studies could usher in a new era in precision cancer treatment and allow the full potential of paclitaxel to be tapped at long last.

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ABBREVIATIONS

APC	adenomatous polyposis coli
CLIP-170	cytoplasmic linker protein 170
CYLD	cyllindromatosis
EB	end-binding protein
MAP	microtubule-associated protein
MCAK	mitotic centromere-associated kinesin

REFERENCES

1. Gray, JA. Textbook of Experimental Cytology. Cambridge, UK: Cambridge University Press; 2013.
2. Inoué S. Polarization optical studies of the mitotic spindle. *Chromosoma*. 1953; 5(1):487–500. [PubMed: 13082662]
3. Inoue S. Microtubule dynamics in cell division: Exploring living cells with polarized light microscopy. *Annu Rev Cell Dev Biol*. 2008; 24:1–28. [PubMed: 18631099]
4. Slautterback DB. Cytoplasmic microtubules: I. Hydra. *J Cell Biol*. 1963; 18(2):367–388. [PubMed: 14079495]
5. Walczak CE, Cai S, Khodjakov A. Mechanisms of chromosome behaviour during mitosis. *Nat Rev Mol Cell Biol*. 2010; 11(2):91–102. [PubMed: 20068571]

6. Zhou J, Panda D, Landen JW, Wilson L, Joshi HC. Minor alteration of microtubule dynamics causes loss of tension across kinetochore pairs and activates the spindle checkpoint. *J Biol Chem.* 2002; 277(19):17200–17208. [PubMed: 11864974]
7. van der Vaart B, Akhmanova A, Straube A. Regulation of microtubule dynamic instability. *Biochem Soc Trans.* 2009; 37(Pt 5):1007–1013. [PubMed: 19754441]
8. Zhou J, Giannakakou P. Targeting microtubules for cancer chemotherapy. *Curr Med Chem Anticancer Agents.* 2005; 5(1):65–71. [PubMed: 15720262]
9. Ferlini C, Cicchillitti L, Raspaglio G, Bartollino S, Cimitan S, Bertucci C, Mozzetti S, Gallo D, Persico M, Fattorusso C, Campiani G, Scambia G. Paclitaxel directly binds to Bcl-2 and functionally mimics activity of Nur77. *Cancer Res.* 2009; 69(17):6906–6914. [PubMed: 19671798]
10. Le Grand M, Rovini A, Bourgarel-Rey V, Honore S, Bastonero S, Braguer D, Carre M. ROS-mediated EB1 phosphorylation through Akt/GSK3beta pathway: Implication in cancer cell response to microtubule-targeting agents. *Oncotarget.* 2014; 5(10):3408–3423. [PubMed: 24930764]
11. Jiang L, Li L, He X, Yi Q, He B, Cao J, Pan W, Gu Z. Overcoming drug-resistant lung cancer by paclitaxel loaded dual-functional liposomes with mitochondria targeting and pH-response. *Biomaterials.* 2015; 52:126–139. [PubMed: 25818419]
12. Zhou J, Zhao WY, Ma X, Ju RJ, Li XY, Li N, Sun MG, Shi JF, Zhang CX, Lu WL. The anticancer efficacy of paclitaxel liposomes modified with mitochondrial targeting conjugate in resistant lung cancer. *Biomaterials.* 2013; 34(14):3626–3638. [PubMed: 23422592]
13. Weissig V. Mitochondria-specific nanocarriers for improving the proapoptotic activity of small molecules. *Methods Enzymol.* 2012; 508:131–155. [PubMed: 22449924]
14. Biswas S, Dodwadkar NS, Deshpande PP, Torchilin VP. Liposomes loaded with paclitaxel and modified with novel triphenylphosphonium-PEG-PE conjugate possess low toxicity, target mitochondria and demonstrate enhanced antitumor effects in vitro and in vivo. *J Control Release.* 2012; 159(3):393–402. [PubMed: 22286008]
15. Prota AE, Bargsten K, Zurwerra D, Field JJ, Diaz JF, Altmann KH, Steinmetz MO. Molecular mechanism of action of microtubule-stabilizing anticancer agents. *Science.* 2013; 339(6119):587–590. [PubMed: 23287720]
16. Wosnitzer MS, Domingo-Domenech J, Castillo-Martin M, Ritch C, Mansukhani M, Petrylack DP, Benson MC, McKiernan JM, Cordon-Cardo C. Predictive value of microtubule associated proteins tau and stathmin in patients with nonmuscle invasive bladder cancer receiving adjuvant intravesical taxane therapy. *J Urol.* 2011; 186(5):2094–2100. [PubMed: 21944130]
17. Sun R, Liu Z, Wang L, Lv W, Liu J, Ding C, Yuan Y, Lei G, Xu C. Overexpression of stathmin is resistant to paclitaxel treatment in patients with non-small cell lung cancer. *Tumour Biol.* 2015 Apr 18. [Epub ahead of print]. PMID: 25894372.
18. Yu J, Gao J, Lu Z, Gong J, Li Y, Dong B, Li Z, Zhang X, Shen L. Combination of microtubule associated protein-tau and beta-tubulin III predicts chemosensitivity of paclitaxel in patients with advanced gastric cancer. *Eur J Cancer.* 2014; 50(13):2328–2335. [PubMed: 25016949]
19. Sun X, Shi X, Liu M, Li D, Zhang L, Liu X, Zhou J. Mdp3 is a novel microtubule-binding protein that regulates microtubule assembly and stability. *Cell Cycle.* 2011; 10(22):3929–3937. [PubMed: 22142902]
20. Tala, Sun X, Chen J, Zhang L, Liu N, Zhou J, Li D, Liu M. Microtubule stabilization by Mdp3 is partially attributed to its modulation of HDAC6 in addition to its association with tubulin and microtubules. *PLoS One.* 2014; 9(3):e90932. [PubMed: 24614595]
21. Tala, Xie S, Sun X, Ran J, Zhang L, Li D, Liu M, Bao G, Zhou J. Microtubule-associated protein Mdp3 promotes breast cancer growth and metastasis. *Theranostics.* 2014; 4(10):1052–1061. [PubMed: 25161703]
22. Gao J, Huo L, Sun X, Liu M, Li D, Dong JT, Zhou J. The tumor suppressor CYLD regulates microtubule dynamics and plays a role in cell migration. *J Biol Chem.* 2008; 283(14):8802–8809. [PubMed: 18222923]
23. Sun L, Gao J, Huo L, Sun X, Shi X, Liu M, Li D, Zhang C, Zhou J. Tumour suppressor CYLD is a negative regulator of the mitotic kinase Aurora-B. *J Pathol.* 2010; 221(4):425–432. [PubMed: 20593489]

24. Gao J, Sun L, Huo L, Liu M, Li D, Zhou J. CYLD regulates angiogenesis by mediating vascular endothelial cell migration. *Blood*. 2010; 115(20):4130–4137. [PubMed: 20194890]
25. Yang Y, Liu M, Li D, Ran J, Gao J, Suo S, Sun SC, Zhou J. CYLD regulates spindle orientation by stabilizing astral microtubules and promoting dishevelled-NuMA-dynein/dynactin complex formation. *Proc Natl Acad Sci USA*. 2014; 111(6):2158–2163. [PubMed: 24469800]
26. Yang Y, Ran J, Liu M, Li D, Li Y, Shi X, Meng D, Pan J, Ou G, Aneja R, Sun SC, Zhou J. CYLD mediates ciliogenesis in multiple organs by deubiquitinating Cep70 and inactivating HDAC6. *Cell Res*. 2014; 24(11):1342–1353. [PubMed: 25342559]
27. Wickstrom SA, Masoumi KC, Khochbin S, Fassler R, Massoumi R. CYLD negatively regulates cell-cycle progression by inactivating HDAC6 and increasing the levels of acetylated tubulin. *EMBO J*. 2010; 29(1):131–144. [PubMed: 19893491]
28. Yang Y, Ran J, Sun L, Sun X, Luo Y, Yan B, Tala, Liu M, Li D, Zhang L, Bao G, Zhou J. CYLD regulates noscapine activity in acute lymphoblastic leukemia via a microtubule-dependent mechanism. *Theranostics*. 2015; 5(7):656–666. [PubMed: 25897332]
29. Drewes G, Ebner A, Preuss U, Mandelkow EM, Mandelkow E. MARK, a novel family of protein kinases that phosphorylate microtubule-associated proteins and trigger microtubule disruption. *Cell*. 1997; 89(2):297–308. [PubMed: 9108484]
30. Gong CX, Iqbal K. Hyperphosphorylation of microtubule-associated protein tau: A promising therapeutic target for Alzheimer disease. *Curr Med Chem*. 2008; 15(23):2321–2328. [PubMed: 18855662]
31. Evans DB, Rank KB, Bhattacharya K, Thomsen DR, Gurney ME, Sharma SK. Tau phosphorylation at serine 396 and serine 404 by human recombinant tau protein kinase II inhibits tau's ability to promote microtubule assembly. *J Biol Chem*. 2000; 275(32):24977–24983. [PubMed: 10818091]
32. Yoshida H, Hastie CJ, McLauchlan H, Cohen P, Goedert M. Phosphorylation of microtubule-associated protein tau by isoforms of c-Jun N-terminal kinase (JNK). *J Neurochem*. 2004; 90(2):352–358. [PubMed: 15228592]
33. Schwalbe M, Biernat J, Bibow S, Ozenne V, Jensen MR, Kadavath H, Blackledge M, Mandelkow E, Zweckstetter M. Phosphorylation of human Tau protein by microtubule affinity-regulating kinase 2. *Biochemistry*. 2013; 52(50):9068–9079. [PubMed: 24251416]
34. Rouzier R, Rajan R, Wagner P, Hess KR, Gold DL, Stec J, Ayers M, Ross JS, Zhang P, Buchholz TA, Kuerer H, Green M, Arun B, Hortobagyi GN, Symmans WF, Pusztai L. Microtubule-associated protein tau: A marker of paclitaxel sensitivity in breast cancer. *Proc Natl Acad Sci USA*. 2005; 102(23):8315–8320. [PubMed: 15914550]
35. Wagner P, Wang B, Clark E, Lee H, Rouzier R, Pusztai L. Microtubule Associated Protein (MAP)-Tau: A novel mediator of paclitaxel sensitivity in vitro and in vivo. *Cell Cycle*. 2005; 4(9):1149–1152. [PubMed: 16103753]
36. Ross JL, Santangelo CD, Makrides V, Fyngenson DK. Tau induces cooperative Taxol binding to microtubules. *Proc Natl Acad Sci USA*. 2004; 101(35):12910–12915. [PubMed: 15326286]
37. Hernandez F, Garcia-Garcia E, Avila J. Microtubule depolymerization and tau phosphorylation. *J Alzheimers Dis*. 2013; 37(3):507–513. [PubMed: 23948896]
38. Wang Y, Feng Y, Fu Q, Li L. Panax notoginsenoside Rb1 ameliorates Alzheimer's disease by upregulating brain-derived neurotrophic factor and downregulating Tau protein expression. *Exp Ther Med*. 2013; 6(3):826–830. [PubMed: 24137274]
39. Bauer JA, Chakravarthy AB, Rosenbluth JM, Mi D, Seeley EH, De Matos Granja-Ingram N, Olivares MG, Kelley MC, Mayer IA, Meszoely IM, Means-Powell JA, Johnson KN, Tsai CJ, Ayers GD, Sanders ME, Schneider RJ, Formenti SC, Caprioli RM, Pietenpol JA. Identification of markers of taxane sensitivity using proteomic and genomic analyses of breast tumors from patients receiving neoadjuvant paclitaxel and radiation. *Clin Cancer Res*. 2010; 16(2):681–690. [PubMed: 20068102]
40. Bhat KM, Maddodi N, Shashikant C, Setaluri V. Transcriptional regulation of human MAP2 gene in melanoma: Role of neuronal bHLH factors and Notch1 signaling. *Nucleic Acids Res*. 2006; 34(13):3819–3832. [PubMed: 16916793]

41. Marklund U, Larsson N, Gradin HM, Brattsand G, Gullberg M. Oncoprotein 18 is a phosphorylation-responsive regulator of microtubule dynamics. *EMBO J.* 1996; 15(19):5290–5298. [PubMed: 8895574]
42. Mistry SJ, Atweh GF. Stathmin inhibition enhances okadaic acid-induced mitotic arrest: A potential role for stathmin in mitotic exit. *J Biol Chem.* 2001; 276(33):31209–31215. [PubMed: 11418586]
43. Amayed P, Pantaloni D, Carlier MF. The effect of stathmin phosphorylation on microtubule assembly depends on tubulin critical concentration. *J Biol Chem.* 2002; 277(25):22718–22724. [PubMed: 11956188]
44. Alli E, Yang JM, Ford JM, Hait WN. Reversal of stathmin-mediated resistance to paclitaxel and vinblastine in human breast carcinoma cells. *Mol Pharmacol.* 2007; 71(5):1233–1240. [PubMed: 17272681]
45. Mistry SJ, Bank A, Atweh GF. Synergistic antiangiogenic effects of stathmin inhibition and taxol exposure. *Mol Cancer Res.* 2007; 5(8):773–782. [PubMed: 17670914]
46. Alli E, Bash-Babula J, Yang JM, Hait WN. Effect of stathmin on the sensitivity to antimicrotubule drugs in human breast cancer. *Cancer Res.* 2002; 62(23):6864–6869. [PubMed: 12460900]
47. Su D, Smith SM, Preti M, Schwartz P, Rutherford TJ, Menato G, Danese S, Ma S, Yu H, Katsaros D. Stathmin and tubulin expression and survival of ovarian cancer patients receiving platinum treatment with and without paclitaxel. *Cancer.* 2009; 115(11):2453–2463. [PubMed: 19322891]
48. Mistry SJ, Atweh GF. Therapeutic interactions between stathmin inhibition and chemotherapeutic agents in prostate cancer. *Mol Cancer Ther.* 2006; 5(12):3248–3257. [PubMed: 17172428]
49. Iancu C, Mistry SJ, Arkin S, Atweh GF. Taxol and anti-stathmin therapy: A synergistic combination that targets the mitotic spindle. *Cancer Res.* 2000; 60(13):3537–3541. [PubMed: 10910066]
50. Wu Y, Tang M, Weng X, Yang L, Xu W, Yi W, Gao J, Bode AM, Dong Z, Cao Y. A combination of paclitaxel and siRNA-mediated silencing of Stathmin inhibits growth and promotes apoptosis of nasopharyngeal carcinoma cells. *Cell Oncol (Dordr).* 2014; 37(1):53–67. [PubMed: 24306928]
51. Werner HM, Trovik J, Halle MK, Wik E, Akslen LA, Birkeland E, Bredholt T, Tangen IL, Krakstad C, Salvesen HB. Stathmin protein level, a potential predictive marker for taxane treatment response in endometrial cancer. *PLoS One.* 2014; 9(2):e90141. [PubMed: 24587245]
52. Howard J, Hyman AA. Dynamics and mechanics of the microtubule plus end. *Nature.* 2003; 422(6933):753–758. [PubMed: 12700769]
53. Akhmanova A, Steinmetz MO. Tracking the ends: A dynamic protein network controls the fate of microtubule tips. *Nat Rev Mol Cell Biol.* 2008; 9(4):309–322. [PubMed: 18322465]
54. Honnappa S, Gouveia SM, Weisbrich A, Damberger FF, Bhavesh NS, Jawhari H, Grigoriev I, van Rijssel FJ, Buey RM, Lawera A, Jelesarov I, Winkler FK, Wuthrich K, Akhmanova A, Steinmetz MO. An EB1-binding motif acts as a microtubule tip localization signal. *Cell.* 2009; 138(2):366–376. [PubMed: 19632184]
55. Li D, Gao J, Yang Y, Sun L, Suo S, Luo Y, Shui W, Zhou J, Liu M. CYLD coordinates with EB1 to regulate microtubule dynamics and cell migration. *Cell Cycle.* 2014; 13(6):974–983. [PubMed: 24552808]
56. Li D, Xie S, Ren Y, Huo L, Gao J, Cui D, Liu M, Zhou J. Microtubule-associated deacetylase HDAC6 promotes angiogenesis by regulating cell migration in an EB1-dependent manner. *Protein Cell.* 2011; 2(2):150–160. [PubMed: 21359602]
57. Komarova Y, De Groot CO, Grigoriev I, Gouveia SM, Munteanu EL, Schober JM, Honnappa S, Buey RM, Hoogenraad CC, Dogterom M, Borisy GG, Steinmetz MO, Akhmanova A. Mammalian end binding proteins control persistent microtubule growth. *J Cell Biol.* 2009; 184(5):691–706. [PubMed: 19255245]
58. Mohan R, Katrukha EA, Doodhi H, Smal I, Meijering E, Kapitein LC, Steinmetz MO, Akhmanova A. End-binding proteins sensitize microtubules to the action of microtubule-targeting agents. *Proc Natl Acad Sci U S A.* 2013; 110(22):8900–8905. [PubMed: 23674690]
59. Luo Y, Li D, Ran J, Yan B, Chen J, Dong X, Liu Z, Liu R, Zhou J, Liu M. End-binding protein 1 stimulates paclitaxel sensitivity in breast cancer by promoting its actions toward microtubule assembly and stability. *Protein Cell.* 2014; 5(6):469–479. [PubMed: 24748116]

60. Thomas GE, Sreeja JS, Gireesh KK, Gupta H, Manna TK. +TIP EB1 downregulates paclitaxel induced proliferation inhibition and apoptosis in breast cancer cells through inhibition of paclitaxel binding on microtubules. *Int J Oncol.* 2015; 46(1):133–146. [PubMed: 25310526]
61. Dong X, Liu F, Sun L, Liu M, Li D, Su D, Zhu Z, Dong JT, Fu L, Zhou J. Oncogenic function of microtubule end-binding protein 1 in breast cancer. *J Pathol.* 2010; 220(3):361–369. [PubMed: 19967727]
62. Sun L, Gao J, Dong X, Liu M, Li D, Shi X, Dong JT, Lu X, Liu C, Zhou J. EB1 promotes Aurora-B kinase activity through blocking its inactivation by protein phosphatase 2A. *Proc Natl Acad Sci USA.* 2008; 105(20):7153–7158. [PubMed: 18477699]
63. Sun X, Li D, Yang Y, Ren Y, Li J, Wang Z, Dong B, Liu M, Zhou J. Microtubule-binding protein CLIP-170 is a mediator of paclitaxel sensitivity. *J Pathol.* 2012; 226(4):666–673. [PubMed: 21989536]
64. Ganguly A, Yang H, Pedroza M, Bhattacharya R, Cabral F. Mitotic centromere-associated kinesin (MCAK) mediates paclitaxel resistance. *J Biol Chem.* 2011; 286(42):36378–36384. [PubMed: 21903575]
65. Ganguly A, Yang H, Cabral F. Overexpression of mitotic centromere-associated kinesin stimulates microtubule detachment and confers resistance to paclitaxel. *Mol Cancer Ther.* 2011; 10(6):929–937. [PubMed: 21471284]
66. Jiang K, Wang J, Liu J, Ward T, Wordeman L, Davidson A, Wang F, Yao X. TIP150 interacts with and targets MCAK at the microtubule plus ends. *EMBO Rep.* 2009; 10(8):857–865. [PubMed: 19543227]
67. Yang F, Jiang Q, Zhao J, Ren Y, Sutton MD, Feng J. Parkin stabilizes microtubules through strong binding mediated by three independent domains. *J Biol Chem.* 2005; 280(17):17154–17162. [PubMed: 15737990]
68. Fujiwara M, Marusawa H, Wang HQ, Iwai A, Ikeuchi K, Imai Y, Kataoka A, Nukina N, Takahashi R, Chiba T. Parkin as a tumor suppressor gene for hepatocellular carcinoma. *Oncogene.* 2008; 27(46):6002–6011. [PubMed: 18574468]
69. Yeo CW, Ng FS, Chai C, Tan JM, Koh GR, Chong YK, Koh LW, Foong CS, Sandanaraj E, Holbrook JD, Ang BT, Takahashi R, Tang C, Lim KL. Parkin pathway activation mitigates glioma cell proliferation and predicts patient survival. *Cancer Res.* 2012; 72(10):2543–2553. [PubMed: 22431710]
70. Wang H, Liu B, Zhang C, Peng G, Liu M, Li D, Gu F, Chen Q, Dong JT, Fu L, Zhou J. Parkin regulates paclitaxel sensitivity in breast cancer via a microtubule-dependent mechanism. *J Pathol.* 2009; 218(1):76–85. [PubMed: 19214989]
71. Altieri DC. Validating survivin as a cancer therapeutic target. *Nat Rev Cancer.* 2003; 3(1):46–54. [PubMed: 12509766]
72. Li F, Ambrosini G, Chu EY, Plescia J, Tognin S, Marchisio PC, Altieri DC. Control of apoptosis and mitotic spindle checkpoint by survivin. *Nature.* 1998; 396(6711):580–584. [PubMed: 9859993]
73. Cheung CH, Chen HH, Kuo CC, Chang CY, Coumar MS, Hsieh HP, Chang JY. Survivin counteracts the therapeutic effect of microtubule de-stabilizers by stabilizing tubulin polymers. *Mol Cancer.* 2009; 8:43. [PubMed: 19575780]
74. Fetz V, Bier C, Habtemichael N, Schuon R, Schweitzer A, Kunkel M, Engels K, Kovacs AF, Schneider S, Mann W, Stauber RH, Knauer SK. Inducible NO synthase confers chemoresistance in head and neck cancer by modulating survivin. *Int J Cancer.* 2009; 124(9):2033–2041. [PubMed: 19130609]
75. Lu J, Tan M, Huang WC, Li P, Guo H, Tseng LM, Su XH, Yang WT, Treekitkarnmongkol W, Andreeff M, Symmans F, Yu D. Mitotic deregulation by survivin in ErbB2-overexpressing breast cancer cells contributes to Taxol resistance. *Clin Cancer Res.* 2009; 15(4):1326–1334. [PubMed: 19228734]
76. Wu X, Zhi X, Ji M, Wang Q, Li Y, Xie J, Zhao S. Midkine as a potential diagnostic marker in epithelial ovarian cancer for cisplatin/paclitaxel combination clinical therapy. *Am J Cancer Res.* 2015; 5(2):629–638. [PubMed: 25973302]

77. Koo DH, Lee HJ, Ahn JH, Yoon DH, Kim SB, Gong G, Son BH, Ahn SH, Jung KH. Tau and PTEN status as predictive markers for response to trastuzumab and paclitaxel in patients with HER2-positive breast cancer. *Tumour Biol.* 2015; 36(8):5865–5871. [PubMed: 25725586]
78. Razis E, Kalogeras KT, Kotoula V, Eleftheraki AG, Nikitas N, Kronenwett R, Timotheadou E, Christodoulou C, Pectasides D, Gogas H, Wirtz RM, Makatsoris T, Bafaloukos D, Aravantinos G, Televantou D, Pavlidis N, Fountzilas G. Improved outcome of high-risk early HER2 positive breast cancer with high CXCL13-CXCR5 messenger RNA expression. *Clin Breast Cancer.* 2012; 12(3):183–193. [PubMed: 22607768]
79. Bateman NW, Jaworski E, Ao W, Wang G, Litzi T, Dubil E, Marcus C, Conrads KA, Teng PN, Hood BL, Phippen NT, Vasicek LA, McGuire WP, Paz K, Sidransky D, Hamilton CA, Maxwell GL, Darcy KM, Conrads TP. Elevated AKAP12 in paclitaxel-resistant serous ovarian cancer cells is prognostic and predictive of poor survival in patients. *J Proteome Res.* 2015; 14(4):1900–1910. [PubMed: 25748058]
80. Pavlikova N, Bartonova I, Dincakova L, Halada P, Kovar J. Differentially expressed proteins in human breast cancer cells sensitive and resistant to paclitaxel. *Int J Oncol.* 2014; 45(2):822–830. [PubMed: 24898082]
81. Xu H, Dephoure N, Sun H, Zhang H, Fan F, Liu J, Ning X, Dai S, Liu B, Gao M, Fu S, Gygi SP, Zhou C. Proteomic profiling of paclitaxel treated cells identifies a novel mechanism of drug resistance mediated by PDCD4. *J Proteome Res.* 2015; 14(6):2480–2491. [PubMed: 25928036]
82. Lee MC, Lopez-Diaz FJ, Khan SY, Tariq MA, Dayn Y, Vaske CJ, Radenbaugh AJ, Kim HJ, Emerson BM, Pourmand N. Single-cell analyses of transcriptional heterogeneity during drug tolerance transition in cancer cells by RNA sequencing. *Proc Natl Acad Sci USA.* 2014; 111(44):E4726–E4735. [PubMed: 25339441]
83. Pavlikova N, Bartonova I, Balusikova K, Kopperova D, Halada P, Kovar J. Differentially expressed proteins in human MCF-7 breast cancer cells sensitive and resistant to paclitaxel. *Exp Cell Res.* 2015; 333(1):1–10. [PubMed: 25557873]
84. Nogales E, Wolf SG, Downing KH. Structure of the alpha beta tubulin dimer by electron crystallography. *Nature.* 1998; 391(6663):199–203. [PubMed: 9428769]

Biographies

Songbo Xie is a Ph.D. candidate in the laboratory of Professor Jun Zhou in the College of Life Sciences at Nankai University. He received his bachelor's degree from Nankai University in 2005 and his master's degree from Nankai University in 2009. During 2009–2013, he was a scientist and group leader at Pharmaron, Inc., overseeing the drug screening program. At present, he is studying the roles of MBPs in the regulation of cell division, cell motility, and cancer chemotherapeutic resistance.

Angela Ogden is a Ph.D. candidate and Molecular Basis of Disease Fellow in the laboratory of Professor Ritu Aneja in the Department of Biology at Georgia State University. In 2003, she received her bachelor's degree from Emory University. Thereafter, she studied biology and chemistry as a postbaccalaureate student. In 2008, she received an MS in Cellular Molecular Biology and Physiology from Georgia State University, and in 2010 she received an MMSc from the Emory University School of Medicine. At present, she is investigating microtubule-binding drugs that decluster centrosomes, such as noscapinoids and griseofulvin, along with MBPs like human kinesin-related protein (HSET), with an emphasis on their roles in ethnic health disparity.

Ritu Aneja is the director of the Ph.D. program and the interim director of the Molecular Basis of Disease Program in the Department of Biology at Georgia State University. In 1997, she obtained her Ph.D. in Chemistry from the University of Delhi in India. Thereafter,

she served as a postdoctoral fellow at Yale and Emory University. In 2008, she became tenure-track faculty at Georgia State University. One of the principal lines of investigation in her laboratory is the identification and characterization of MBPs that can serve as prognostic and predictive biomarkers in various cancer types, with an emphasis on their utility in risk stratifying patients belonging to ethnic minority groups. Furthermore, her laboratory focuses on discovering “kinder and gentler” chemotherapeutic modalities that target microtubules or MBPs, with the long-term objective of developing agents that are minimally toxic without compromising efficacy. These research efforts constitute significant strides in preclinical cancer research owing to their strong translational relevance, specifically to cancer patient risk stratification and chemotherapeutic development.

Jun Zhou is a professor in the State Key Laboratory of Medicinal Chemical Biology and the College of Life Sciences at Nankai University. He received his bachelor’s degree in Genetics from Fudan University in 1997 and his Ph.D. degree in Biochemistry, Cell and Developmental Biology from Emory University in 2002. Thereafter, he worked at Genentech, Inc., as a postdoctoral fellow and at Emory University as an instructor. In 2005, he returned to China to take a faculty position at Nankai University. During 2014–2015, he was a visiting professor in the Department of Biomedical Engineering at the Georgia Institute of Technology and Emory University. His laboratory focuses on the cytoskeletal basis and signaling mechanism of cancer and novel approaches to cancer diagnosis and therapy, including: (i) regulation of cellular structures, cellular processes, and tissue homeostasis by microtubules and related proteins; (ii) functions of microtubules and related proteins in the pathogenesis and treatment of cancer; and (iii) novel materials and methods for biomedical studies and clinical applications.

Figure 1.

(A) Three-dimensional structure showing that paclitaxel binds to a unique pocket on β -tubulin at the lateral interface between adjacent protofilaments. The structure of the α/β -tubulin dimer (PDB: 1TUB) was obtained from the Protein Data Bank.⁸⁴ (B) A schematic illustration showing that microtubule dynamics are regulated by different types of MBPs. There is a dynamic equilibrium between microtubule polymerization and depolymerization. Canonical MBPs interact with microtubules and promote microtubule polymerization. Microtubule-destabilizing proteins sequester free tubulin or bind to microtubules directly to induce microtubule depolymerization. Microtubule plus end-tracking proteins accumulate at the growing plus ends of microtubules to regulate microtubule dynamics. Noncanonical MBPs act as a scaffold for the interaction of microtubules with other molecules and compartments. (C) A model demonstrating a role for MBPs in regulating cancer cell sensitivity to paclitaxel. Altered expression or posttranslational modification of MBPs modulates the interaction of paclitaxel with microtubules and consequently affects the activities of paclitaxel to disrupt microtubule dynamics and to cause mitotic arrest and apoptosis.

Table I

Regulation of microtubule dynamics and paclitaxel sensitivity by MBPs

Types of MBPs	Roles in microtubule dynamics	Effects on paclitaxel sensitivity
Canonical MBPs		
Tau	Stabilizing microtubules	Tau expression negatively correlates with breast cancer sensitivity to paclitaxel
MAP2	Stabilizing microtubules	High MAP2 expression is associated with improved response to paclitaxel-based chemotherapy
Microtubule-destabilizing proteins		
Stathmin	Sequestering tubulin	Low stathmin expression has synergistic effects with paclitaxel treatment
Microtubule plus end-tracking proteins		
EB1	Promoting microtubule assembly and stabilizing microtubules	EB1 is a vital regulator of paclitaxel sensitivity
CLIP-170	Promoting microtubule assembly and stabilizing microtubules	CLIP-170 expression correlates with pathological complete response to paclitaxel-based chemotherapy
MCAK	Microtubule catastrophe	MCAK is implicated in paclitaxel resistance
Noncanonical MBPs		
Parkin	Binding to the outside of microtubules and promoting microtubule assembly	Higher parkin expression is associated with a better response to paclitaxel-containing chemotherapy
Survivin	Microtubule stabilization	Inhibition of survivin expression increases paclitaxel sensitivity