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β III-tubulin in malignant tumors: unveiling its biological functions, mechanisms and roles in drug resistance



Xiaomeng Xie^{1,2}, Dengyun Zhao², Xuejiao Liu², Xinyi Wang³, Xueli Tian^{4,*}, Dong Joon Kim^{5,6,*} and Zigang Dong^{1,3,7,8,*}

¹ China-US (Henan) Hormel Cancer Institute, Zhengzhou, China

² Medical Research Center, Chest Hospital of Zhengzhou University, Zhengzhou, China

³ Department of Pathology and Pathophysiology, School of Basic Medical Sciences, Zhengzhou University, Zhengzhou, China

⁴ Department of Clinical Research and Translational Medicine, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, China

⁵ Department of Microbiology, College of Medicine, Dankook University, Cheonan, Republic of Korea

⁶ Multidrug-resistant Refractory Cancer Convergence Research Center (MRCRC), Dankook University, Cheonan, Republic of Korea

⁷ Henan Provincial Cooperative Innovation Center for Cancer Chemoprevention, Zhengzhou University, Zhengzhou, China

⁸ Tianjian Laboratory of Advanced Biomedical Sciences, Zhengzhou, China

* Correspondence authors; E-mails: tianxueli0329@163.com (X.T.); djkim407@dankook.ac.kr (D.J.K.); dongzg@zzu.edu.cn (Z.D.).

Highlights:

- Explores the role of TUBB3 in tumor progression and drug resistance.
- Highlights mechanisms underlying TUBB3-mediated chemoresistance.
- Discusses therapeutic strategies targeting TUBB3 in cancer.

Abstract: Microtubules (MTs) are key components of the eukaryotic cytoskeleton, formed by dynamic heterodimers of α - and β -tubulin subunits that constantly assemble and disassemble within cells. Research into microtubule dynamics is crucial due to its relevance in anticancer therapies. In mammals, various β -tubulin subtypes exist, with β III-tubulin (TUBB3) recognized as a significant neuronal biomarker and linked to poor prognosis in cancer patients due to its high expression in tumors. Despite advances in chemotherapy, drug resistance—often attributed to elevated TUBB3 levels—poses significant challenges to effective treatment. Although role of TUBB3 in nervous system is acknowledged, its precise functions and mechanisms in relation to cancer therapies are not fully understood. This review offers an overview of TUBB3's biological function, its distinctions from other β -tubulin isoforms, examines its role in cancer, elucidates its mechanisms of action, and evaluates therapeutic strategies aimed at targeting TUBB3 to combat drug resistance in tumors.



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Keywords: β III-tubulin; malignant tumors; targeted drugs; drug resistance; microtubule dynamics

1. Introduction

Cancer remains a major global health challenge, with an estimated ~20 million new cases and 9.7 million deaths in 2022 and a projected doubling of cancer-related mortality by 2050 [1,2]. Despite advances in systemic therapy, drug resistance continues to undermine clinical benefit [3]. Among the diverse resistance mechanisms, deranged microtubule dynamics have emerged as one of the key contributors to treatment failure [4–7]. Against this backdrop, β III-tubulin (TUBB3) warrants focused attention. TUBB3 is frequently overexpressed across multiple malignancies and has been tied to aggressive phenotypes and reduced therapy responsiveness [8,9]. Distinct from other β -tubulin isoforms, TUBB3 possesses sequence features at the lateral interface that reshape microtubule dynamics and alter cellular responses to microtubule-targeting agents, providing a structural rationale for its context-dependent impact on cancer behavior and treatment outcomes [10–12].

The clinical relevance of TUBB3 extends beyond association to actionability. High TUBB3 expression has been extensively studied as a potential predictive biomarker for taxane-based chemotherapy, with evidence suggesting an association with reduced taxane sensitivity in several tumor types, though findings remain context- and cancer type-dependent. In contrast, agents that bind to the colchicine site frequently retain efficacy in preclinical models of taxane resistance—including those with elevated TUBB3—highlighting the importance of site-specific pharmacology, even though clinical validation of this relationship is still limited [12–14]. In parallel, preclinical studies demonstrate that silencing TUBB3—via siRNA or non-coding RNA modulation—can restore chemosensitivity, curb tumor growth, and temper metastatic traits, thereby nominating TUBB3 and its regulatory circuitry as therapeutic targets [12,15].

This review advances the field by moving beyond a tumor type-specific enumeration toward a mechanistic synthesis of how perturbations in TUBB3's physiological regulation—including mutations, post-translational modifications, and transcriptional or post-transcriptional control—converge on core oncogenic pathways and shape therapeutic responses. We integrate emerging evidence that links TUBB3 to phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling cascades, epithelial–mesenchymal transition (EMT)-associated transcriptional programs, and non-coding RNA regulatory networks, and relate these axes to well-characterized resistance phenotypes. Collectively, we delineate TUBB3 as a context-dependent hub that interconnects cytoskeletal remodeling with cellular stress adaptation and drug response. Finally, we highlight translational opportunities aimed at targeting TUBB3 directly or modulating its upstream regulators and downstream effectors.

2. Structural and functional characterization of TUBB3 as a drug target

2.1. The structure and localization of TUBB3

The TUBB3 gene, located on chromosome 16q24.3, encodes class III β -tubulin through multiple transcript variants. The canonical transcript gives rise to a full-length protein of 450 amino acids, while alternative splicing generates shorter isoforms, such as a 378-amino acid variant lacking part of the 5'

coding region [16]. Structurally, TUBB3 shares the conserved architecture of β -tubulin family members, with an N-terminal domain, an intermediate domain, and a highly flexible acidic C-terminal tail [17]. These domains mediate guanosine triphosphate (GTP) binding, dimerization with α -tubulin, and interactions with microtubule-associated proteins, thereby ensuring dynamic regulation of the microtubule cytoskeleton.

TUBB3 is predominantly localized in the cytoplasm and cytoskeleton but is also found in the nucleus, spindle filaments, and various human tissues, with the highest expression observed in the central nervous system and peripheral nerves [18–21]. RNA expression of TUBB3 is predominantly enriched in brain tissue, with robust single-cell-level expression across inhibitory and excitatory neurons [22,23]. Outside the nervous system, baseline expression is generally low in most epithelial lineages, and reports in pancreatic or gastric epithelial compartments are inconsistent and context-dependent rather than constitutive, with stable constitutive expression only observed in transformed malignant epithelium instead of normal epithelial cells [24]. Furthermore, TUBB3 exhibits brain-enriched expression with robust transcription in neuronal lineages. In peripheral immune cells—including B cells—TUBB3 transcripts are generally low and inconsistently detected across datasets [25,26].

2.2. Biological function of TUBB3

TUBB3 encodes β III-tubulin, a primary component of Microtubules (MTs), which are polymeric cylinders composed of α -tubulin and β -tubulin heterodimers arranged as protofilaments that associate laterally. Fundamentally, as a skeleton protein, TUBB3 plays an important role in maintaining cellular structure (Figure 1). MTs grow by adding GTP-tubulin dimers to their ends, creating a stable cap. The GTPase activity of α -tubulin results in a guanosine diphosphate (GDP)-bound state below this cap [16]. Meanwhile, it is vital for proper microtubule organization during the formation and maintenance of axons and dendrites. TUBB3 is crucial for the proper guidance and maintenance of axons, capable of binding two moles of GTP: one at the exchange site on the β chain and the other at the non-exchange site on the α chain [17]. Moreover, TUBB3 plays a special role in the process of microtubule dynamics, it is involved in the axonal projection from the dorsal root ganglion to the spinal cord, with NTN1/Netrin-1 binding to its receptor UNC-5 netrin receptor C (UNC5C) potentially causing UNC5C dissociation from polymerized TUBB3 in MTs, thereby enhancing microtubule dynamics and promoting axonal retraction [18]. Acetylation on lysine-252 (K252) and phosphorylation of serine residue S172 of β -tubulin slows tubulin incorporation into MTs [27,28]. However, mechanistic origin of the unique activity of β 3 tubulin is that residues at the lateral interface are sufficient to alter microtubule dynamics and response to microtubule targeting agents [10].

Notably, in neurons, TUBB3 expression levels are sensitive to neuronal activity, influencing microtubule growth and motor-driven transport [19,29–32]. TUBB3 supports the movement of vesicles, organelles, and proteins along axons in neurons. This is crucial for synaptic function, neurotransmitter transport, and the overall health and maintenance of neuronal networks. Down-regulation of TUBB3 leads to decreased tubulin polyglutamylation, increased kinesin family member 5C (KIF5C) movement, and enhanced transport of N-Cadherin, a molecule essential for synapse formation and long-term potentiation [19]. TUBB3 also participates in the establishment and maintenance of synapses, playing a role in synaptic vesicle dynamics, which is essential for effective neurotransmission.

In non-neuronal cells, TUBB3 participates in the regulation of the cell cycle, especially during mitosis, where it helps in the formation of the mitotic spindle. This spindle is necessary for chromosome segregation and the proper division of cells [33]. TUBB3 has been shown to be involved in cellular responses to stress, especially in neurons, where its expression can be modulated under conditions like injury, ischemia, or neurodegeneration. In addition, TUBB3 can inhibit human adipose-derived stem cell osteogenesis, and it may be involved in cell metabolism, calcium enrichment, osteoclast differentiation [34].

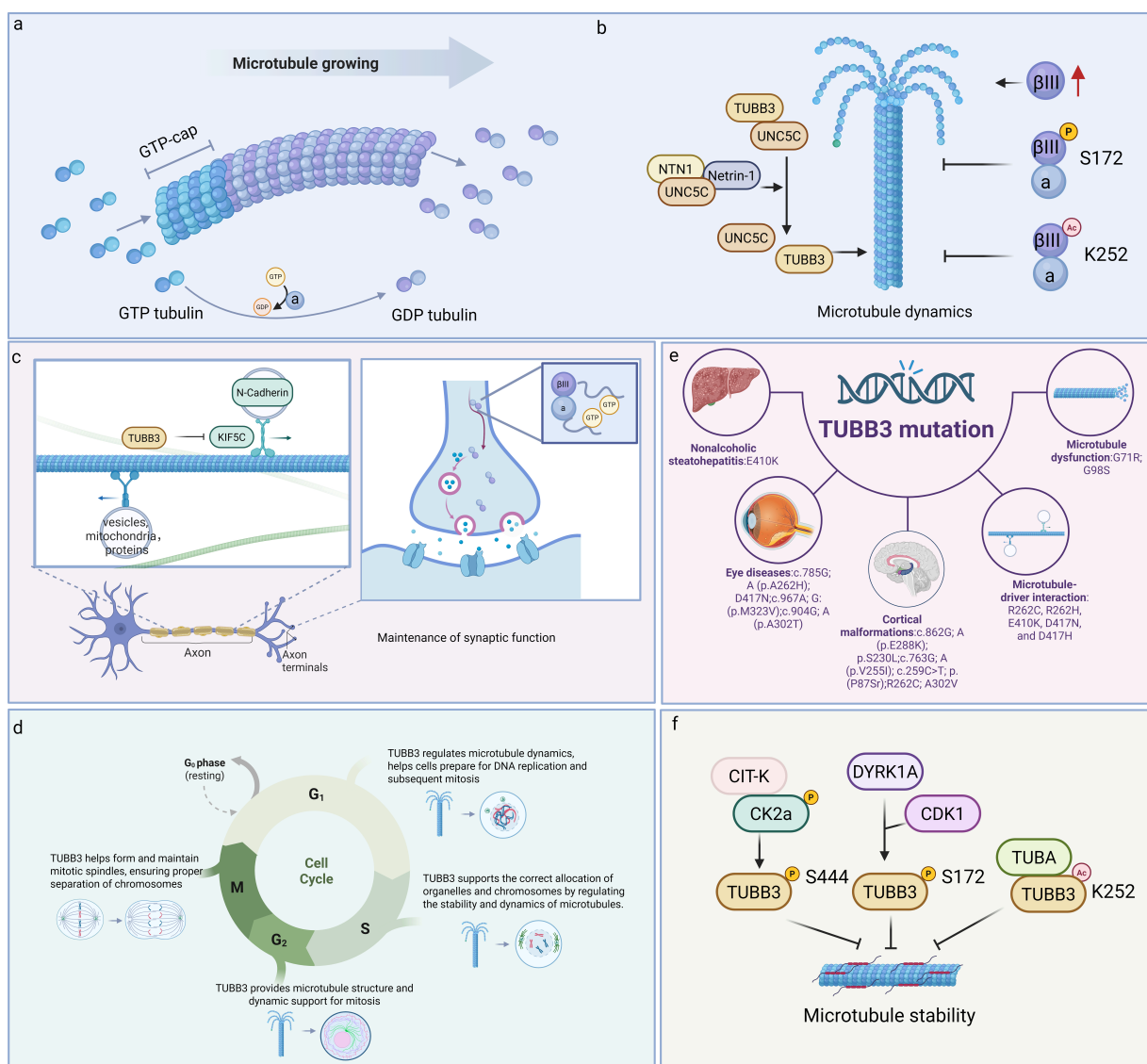


Figure 1. Biological Functions of TUBB3. **(a)** TUBB3 participates in microtubule (MT) growth; **(b)** Mechanisms of TUBB3 inducing microtubule dynamics; **(c)** Role of TUBB3 in guidance and maintenance of synaptic functions; **(d)** Role of TUBB3 in cell cycle regulation; **(e)** Effect of TUBB3 mutation on functions; **(f)** Effect of post-transcriptional modification on TUBB3 function.

2.3. Effect of mutations on TUBB3 function

Mutations in the TUBB3 gene have been extensively studied in the context of neurodevelopmental disorders, where they disrupt axonal guidance, neuronal migration, and cortical development [35,36]. Although these conditions are distinct from cancer, the underlying mechanisms provide important insights into how structural alterations in TUBB3 impact microtubule behavior. Missense mutations frequently cluster in regions critical for lateral interactions between tubulin dimers, thereby modifying polymerization dynamics and impairing interactions with kinesins and microtubule-associated proteins [37–39]. Such changes destabilize MTs and perturb intracellular transport, ultimately affecting cellular polarity and division.

The relevance of these findings for oncology lies in the fact that similar alterations in microtubule dynamics underpin tumor cell proliferation, invasion, and therapeutic resistance. For example, substitutions that reduce tubulin–motor protein binding may mimic adaptive changes seen in drug-resistant cancers, where microtubule remodeling confers survival advantages under chemotherapeutic stress [17]. Moreover, studies of congenital TUBB3 variants demonstrate that even single amino acid changes can profoundly alter microtubule response to external cues, a principle that parallels how tumor cells exploit TUBB3 dysregulation to evade cytotoxic therapies [40–42].

In summary, while most TUBB3 mutations have been described in developmental and neurological disorders, they collectively illustrate the structural sensitivity of TUBB3 and its capacity to reprogram microtubule function. These insights provide a mechanistic framework to understand how dysregulated TUBB3, whether through mutation or aberrant expression, contributes to oncogenic pathways and resistance to microtubule-targeting agents.

2.4. Effect of post-transcriptional modification on TUBB3 function

When α/β -tubulin heterodimers are polymerized into MTs, isotype expression combined with post-transcriptional modification produces microtubule diversity, which is involved in the regulation of microtubule properties and functions in basic cellular processes [43]. Acetylation, phosphorylation, polyglutamylation, and glycanylation are the most common types of post-transcriptional modifications of β -tubulin. The type of acetylation in β -tubulin is K252, and this modification is only found in soluble α - and β -tubulin heterodimers. Acetylation slows tubulin incorporation into MTs by neutralizing the positive charge on K252 and allowing the tubulin heterodimer to adopt a conformation that is unfavorable to tubulin incorporation [27]. Citron kinase (CIT-K) recruits casein kinase 2 α subunit (CK2 α) to midbody TUBB3 to maintain TUBB3 Ser444 phosphorylation and stabilize midbody microtubules [44]. Site-specific phosphorylation (Ser172, Ser339) and N-linked glycosylation (Asn316) of TUBB3 are positively correlated with cellular resistance to taxane-class microtubule-targeted chemotherapies and altered subcellular partitioning of tubulin cytoskeletons, as validated by quantitative proteomic profiling of chemoresistant tumor cell lines [45]. Microtubule kinetics can be affected by the phosphorylation of serine residue S172 of β -tubulin, which is promoted by cyclin-dependent kinase 1 (CDK1) and dual specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) [28,46]. Polyglutamylation and glycanylation have been found in the carboxy-terminal tails of α -tubulin and β -tubulin, and all modifications in the carboxy-terminal tails may regulate the interactions between MTs and related proteins [28]. The movement of drivin-1 on neuronal TUBB3 is increased by polyglutamylation [47].

In summary, TUBB3 contributes to cellular physiology through multiple regulatory layers, including its fundamental role in microtubule dynamics, its disruption by pathogenic mutations, and its fine-tuning via post-translational modifications. While each of these aspects has been traditionally examined in isolation, they collectively shape the functional state of TUBB3 and determine its broader impact on cancer biology. Mutations can alter the intrinsic properties of MTs, post-translational modifications (PTMs) can dynamically regulate stability and interactions, and aberrant expression can amplify these effects in tumor contexts. To better understand the significance of TUBB3 in malignancies, it is therefore essential to integrate these diverse alterations into a unified framework that links molecular changes to pathway-level consequences. This perspective provides the basis for the following section, which highlights how TUBB3 alterations converge to influence cancer pathways and therapeutic responses.

2.5. TUBB3 alterations in cancer biology

Although TUBB3 mutations, PTMs, and aberrant expression have been studied separately, these alterations are now recognized to converge on a discrete set of five cancer-relevant pathways—primarily microtubule dynamics, PI3K/AKT signaling, MAPK/ERK signaling, EMT, and apoptosis regulation [28]. Mutations in TUBB3 alter microtubule dynamics and impair neuronal guidance mechanisms, while in cancer they may disrupt cytoskeletal organization and signaling fidelity [17,48]. Similarly, PTMs such as phosphorylation, acetylation, and polyglutamylation fine-tune TUBB3's incorporation into MTs and its interaction with regulatory proteins, thereby modulating mitotic spindle integrity, cell cycle progression, and stress adaptation [49,50]. Aberrant overexpression of TUBB3 across multiple tumor types further amplifies these effects by stabilizing MTs under therapeutic pressure and enabling activation of survival signaling pathways, particularly through PI3K/AKT and MAPK/ERK axes [48].

Taken together, these distinct layers of regulation—genetic, epigenetic, and post-translational—form a hierarchical framework in which TUBB3 serves as a central node connecting microtubule dynamics to oncogenic signaling. This integrated perspective clarifies why TUBB3 alterations, though heterogeneous in origin, consistently associate with aggressive phenotypes and drug resistance. It also highlights that the clinical significance of TUBB3 cannot be fully appreciated by examining mutations, PTMs, or expression patterns in isolation, but rather by understanding how they collectively remodel key pathways in cancer biology [12,48].

3. Comparative analysis of TUBB3 and other β -tubulin isoforms

At a broader level, the therapeutic value of TUBB3 must also be interpreted within the context of the β -tubulin isoform family. Understanding how TUBB3 functionally diverges from other isoforms such as TUBB2A, TUBB4, and TUBB6 is crucial, as these isoforms may exert compensatory or antagonistic roles in drug response. Therefore, here we will comparatively analyze TUBB3 and its related isoforms, highlighting the structural, functional, and clinical distinctions that ultimately shape therapeutic opportunities.

3.1. The β -tubulin isoform landscape

The human β -tubulin family consists of multiple isotypes encoded by distinct genes, including TUBB (β I), TUBB1, TUBB2A, TUBB2B, TUBB3 (β III), TUBB4A, TUBB4B, TUBB6, and TUBB8 [28]. These isotypes assemble with α -tubulins into conserved α/β heterodimers, forming the basic structural unit of MTs [51]. Despite this shared architecture, sequence divergence—particularly within the C-terminal tails and lateral contact regions (β -M-loop)—modulates microtubule dynamics, protofilament number, and interactions with microtubule-associated proteins (MAPs) and motor proteins [47,52]. Additionally, PTMs of tubulin and the “tubulin code” further regulate microtubule behavior by influencing polymer stability, depolymerization dynamics, and interactions with cellular signaling networks [52]. This molecular diversity underpins both functional specialization and disease-relevant alterations across various cell types.

For example, TUBB3 has been implicated in resistance to microtubule-targeting agents (MTAs) such as taxanes, while its overexpression in tumors is associated with increased tumor aggressiveness and poor prognosis [53–55]. On the other hand, mutations in TUBB4A are linked to hypomyelination disorders, such as hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) syndrome, underscoring the importance of specific β -tubulin isotypes in neurological diseases [56]. Moreover, TUBB2B mutations are associated with cortical malformations and cerebral development disorders, demonstrating the profound effects of tubulin isotype diversity on neurodevelopmental processes [57].

These observations highlight the evolutionary redundancy of β -tubulin isotypes, which ensures cytoskeletal stability, but also suggest that subtle amino acid differences in tubulin isotypes allow for functional specialization. This is particularly evident in the context of chemotherapeutic resistance and cellular differentiation, where specific isotypes serve as critical modulators of microtubule integrity and drug sensitivity [58]. In summary, the β -tubulin family exhibits a remarkable degree of molecular heterogeneity, which contributes to the regulation of microtubule dynamics and isoform-specific roles in both normal physiology and disease pathology.

3.2. Tissue-specific expression and baseline functions

The β -tubulin family exhibits isoform-specific expression patterns across tissues, reflecting their fundamental and specialized cellular functions (Figure 2). TUBB (β I) and TUBB1 are broadly expressed in proliferative and metabolically active tissues, with TUBB1 showing enrichment in megakaryocytes and platelets, where it contributes to thrombopoiesis and platelet formation [28,59,60]. In contrast, TUBB2A and TUBB2B are predominantly expressed in the central nervous system (CNS), where they regulate neuronal migration, differentiation, and microtubule stability, playing critical roles during neurodevelopment [17,61,62]. TUBB3, highly enriched in neurons and testicular germ cells, is indispensable for axon guidance, axonal transport, and synaptic plasticity. Importantly, ectopic TUBB3 upregulation in cancers has been consistently associated with taxane resistance and adverse prognosis, underscoring its significance as both a biomarker and therapeutic target [42,55,63]. TUBB4A, the major neuronal isoform in the cerebellum and cortex, is essential for maintaining myelin integrity, and its mutations cause H-ABC syndrome [12,64]. TUBB4B is more broadly expressed, including in vascular and stromal tissues, where it supports cellular migration and angiogenesis [65]. TUBB6 is expressed in multiple tissues, including brain, kidney, and muscle, and is linked to dynamic instability of MTs, cell division, and

differentiation [66]. Finally, TUBB8 is an oocyte-specific isoform critical for meiotic spindle assembly [67]; mutations in TUBB8 are a major cause of human oocyte maturation arrest and infertility [68].

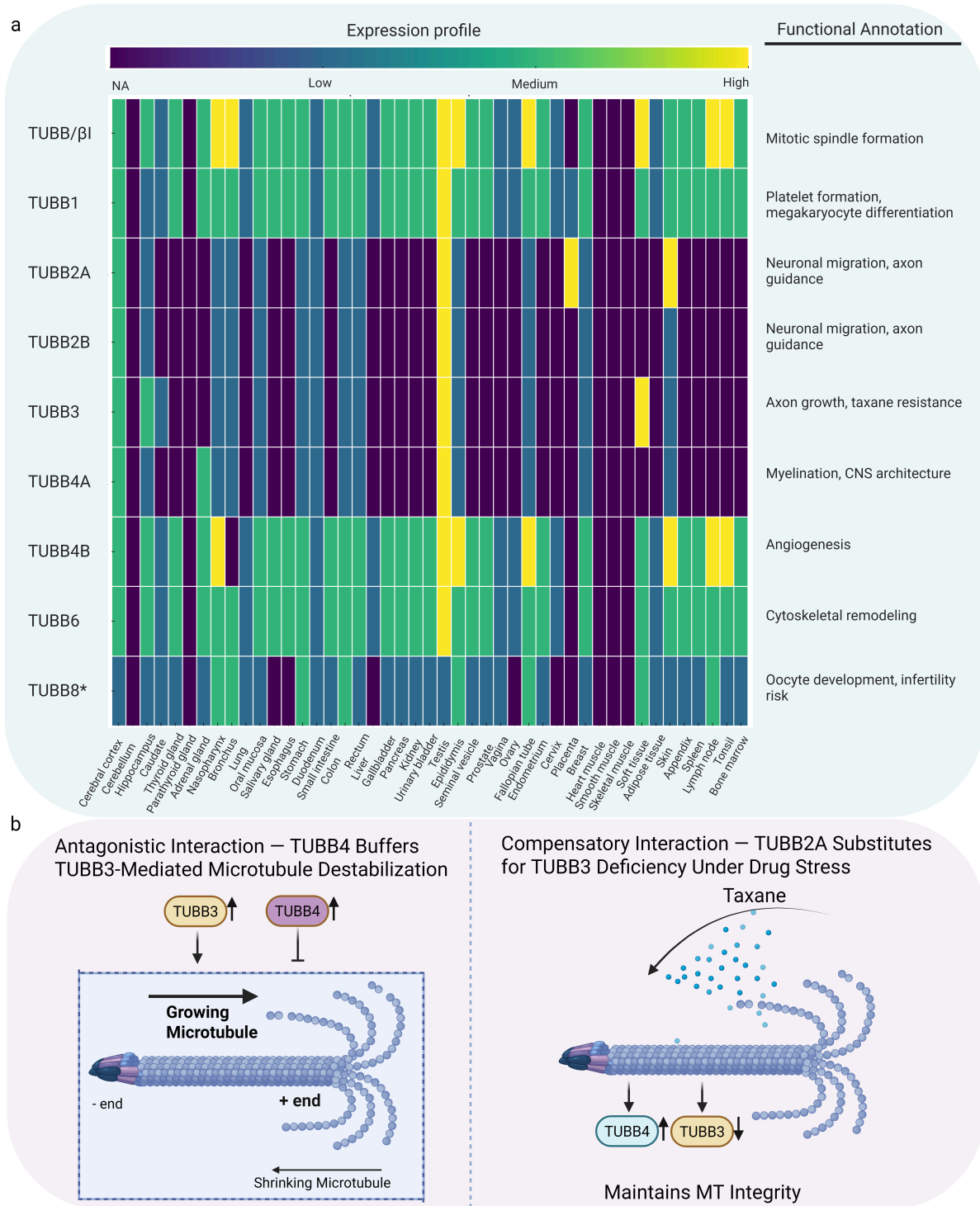


Figure 2. Functional Diversity and Inter-Isoform Interactions within the β -Tubulin Family. **(a)** Tissue-specific expression and functional roles of β -Tubulin isoforms. Human tissue expression data (obtained from protein consensus tissue gene data from the Human Protein Atlas) is presented as a heat map. Protein expression data is shown for each of the 44 tissues based on knowledge-based annotation. Color coding is based on tissue groups, each consisting of tissues with shared functional features. *TUBB8 expression data is summarized by immunohistochemistry primary data; **(b)** Antagonistic and Compensatory Interactions Between β -Tubulin Isoforms.

A degree of functional redundancy exists among isoforms, particularly between TUBB2A and TUBB4, where compensatory upregulation helps buffer against cytoskeletal disruption. Knockdown studies in neuronal and epithelial systems confirm that depletion of one isoform can be partially rescued by the induction of the other [28,61,69]. At the baseline level, all β -tubulin isoforms share core roles in microtubule polymerization, stability, and structural maintenance, supporting fundamental processes such as mitosis, intracellular transport, and cellular morphology. Beyond these, isoform-specific features endow specialized functions, ranging from neuronal plasticity and axonogenesis (TUBB3) to fertility regulation (TUBB8) [70–72]. Notably, while most isoforms in malignant cells sustain the proliferative cytoskeletal framework, TUBB3 uniquely acts as a stress-responsive isoform, shifting from its physiological neuronal role to a cancer-associated survival mechanism that promotes drug resistance and poor clinical outcomes [12,42,55].

3.3. Structural distinctions and drug interactions

A defining structural feature of TUBB3 lies in its unique amino acid substitutions within lateral interaction domains, including regions such as the M-loop and H6–H7 helices of the tubulin dimer. These subtle alterations modulate protofilament lateral contacts and tubulin conformational flexibility, resulting in accelerated dynamic instability, enhanced adaptability under depolymerizing stress, and altered interactions with MAPs [59,73,74]. Importantly, these sequence variations also reduce the binding affinity of several MTAs, particularly taxanes (e.g., paclitaxel, docetaxel) and vinca alkaloids (e.g., vincristine, vinblastine) [73,75–79]. As a consequence, overexpression of TUBB3 has been strongly correlated with clinical drug resistance across multiple cancer types [55,80].

By contrast, other isoforms such as TUBB2A and TUBB4A/4B maintain more conserved lateral interaction domains and do not significantly alter drug-binding kinetics. Consequently, their expression does not independently predict therapeutic outcomes or resistance to MTAs. This isoform-specific structural distinction explains why TUBB3 is consistently regarded as a predictive marker for chemotherapy response, whereas other β -tubulin isoforms primarily function in maintaining baseline cytoskeletal dynamics without directly modulating drug sensitivity [11,12].

3.4. Isoform interplay: antagonism and compensation

Accumulating evidence from both *in vitro* studies and patient-derived tumor samples suggests that β -tubulin isoforms do not act in isolation but can engage in antagonistic or compensatory interactions. For example, TUBB4 has been shown to partially counteract the microtubule-destabilizing effects of TUBB3, thereby buffering excessive cytoskeletal dynamics and stabilizing microtubule networks [11,59]. Likewise, upregulation of TUBB2A can substitute, at least in part, for TUBB3 deficiency, maintaining microtubule integrity under selective pressure such as drug treatment [23,81]. These interactions highlight the plasticity of the tubulin network in adapting to environmental and therapeutic stress.

Nevertheless, such compensatory mechanisms are incomplete and context-dependent. Importantly, among all isoforms, only TUBB3 demonstrates a consistent and reproducible association with EMT, chemoresistance, and aggressive tumor behavior across diverse cancer types [42,55,82]. This distinctive clinicopathological correlation underscores the non-redundant role of TUBB3 in malignancy, distinguishing

it from other isoforms whose contributions are limited to cytoskeletal homeostasis without directly driving oncogenic phenotypes.

3.5. Clinical and therapeutic implications

The clinical significance of β -tubulin isoform diversity is underscored by its impact on both treatment efficacy and toxicity. Conventional pan-tubulin inhibitors (e.g., paclitaxel, docetaxel, vincristine) disrupt MTs indiscriminately across all isoforms, leading to potent antitumor activity but also considerable systemic toxicities—particularly peripheral neuropathy—due to collateral damage of neuron-enriched isoforms such as TUBB3 [83,84]. These limitations have driven efforts toward isoform-selective therapeutic strategies.

Among isoforms, TUBB3 stands out as both a prognostic biomarker and a therapeutic target. Its selective upregulation in cancers, but limited expression in most normal tissues, positions it as an attractive node for precision oncology. Preclinical studies suggest that targeting TUBB3 itself or its stress-responsive regulatory networks—epithelial mesenchymal transition (EMT) transcription factors—can sensitize tumors to MTAs without broadly impairing essential housekeeping isoforms [42,55]. Moreover, strategies aimed at disrupting TUBB3-mediated microtubule dynamics, such as small molecules or antisense oligonucleotides, are being explored as a means to attenuate tumor aggressiveness while minimizing systemic toxicity [85].

Thus, TUBB3 represents not only a marker of poor prognosis and chemoresistance but also a therapeutic entry point for designing next-generation precision medicine approaches. By exploiting the cancer-specific induction of TUBB3 while sparing ubiquitous isoforms, such strategies could mitigate toxicity and improve therapeutic outcomes, marking a potential paradigm shift in the development of tubulin-targeted therapies.

4. TUBB3 in cancer: from overexpression to chemoresistance

In normal tissues, TUBB3 expression is largely restricted to neurons and testicular cells [9], where it serves as a marker of neuronal differentiation. In malignant tumors, however, TUBB3 is frequently aberrantly expressed and exerts diverse, sometimes contradictory, prognostic implications. To provide clarity, we discuss its role by grouping tumors according to organ systems, which facilitates the identification of shared mechanisms and context-specific differences.

To evaluate TUBB3 expression and its prognostic significance across cancer types, RNA-sequencing data and corresponding clinical information were retrieved from The Cancer Genome Atlas (TCGA) database via the Gene Expression Profiling Interactive Analysis 2 (GEPIA2, <http://gepia2.cancer-pku.cn/>) platform. We found that TUBB3 shows abnormally highly expression in skin cutaneous melanoma (SKCM) and low expression in testicular germ cell tumor (TGCT) (Figure 3a). Then we searched the prognosis role of TUBB3 in tumors, and found that it is double-edged in different tumor types, which is associated with poor prognosis in adrenocortical carcinoma (ACC), glioblastoma multiforme (GBM) and uveal melanoma (UVM), while good prognosis in kidney chromophobe (KICH) (Figure 3b). Since TUBB3 presents differently in different tumors, we reviewed the expression and prognosis of TUBB3 in all tumor types (Figure 3c).

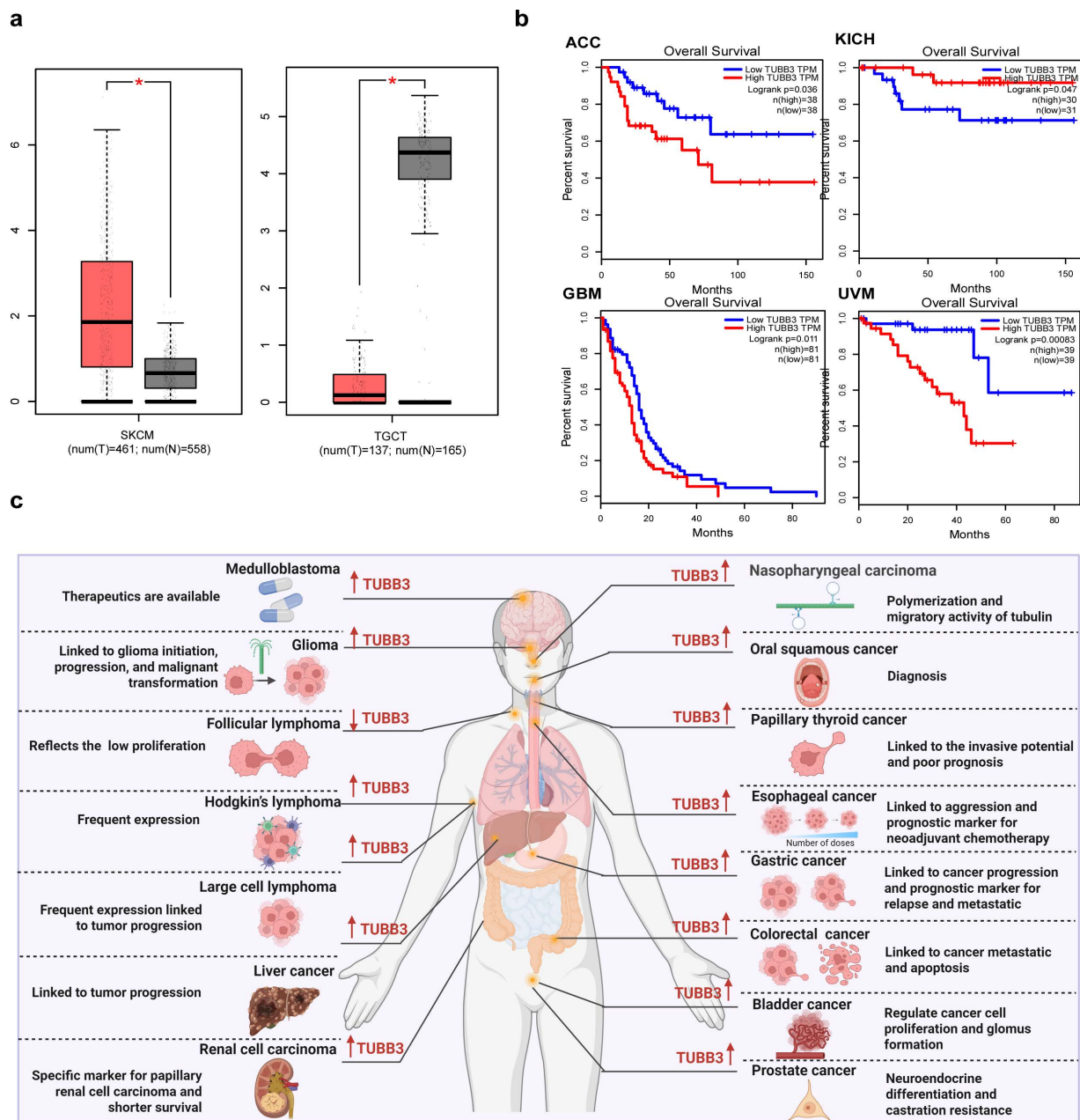


Figure 3. Role of TUBB3 in cancers. **(a)** The expression of TUBB3 in SKCM and TGCT. Differential expression analysis between tumor and normal tissues was performed using one-way analysis of variance (ANOVA) with a threshold of $|\log_2FC| > 1$ and $q\text{-value} < 0.01$; **(b)** The prognosis of TUBB3 in ACC, KICH, GBM and UVM. For survival analysis, patients were stratified into high- and low-TUBB3 expression groups based on the median expression value as the cutoff. Overall survival (OS) curves were estimated using the Kaplan-Meier method, and statistical significance was assessed by the two-sided log-rank test. A $P\text{-value} < 0.05$ was considered statistically significant; **(c)** Summary of TUBB3 expression patterns and prognostic roles across various cancer types.

4.1. Imbalance of TUBB3 expression in tumors

(1) Central Nervous System Tumors

TUBB3 is highly expressed in glioblastoma multiforme, whereas in medulloblastoma, TUBB3 expression is markedly heterogeneous, with elevated levels predominantly observed in specific molecular

subgroups rather than uniformly across all tumors [86,87]. In these contexts, excessive TUBB3 expression disrupts microtubule dynamics and supports malignant progression [88]. By contrast, in certain lymphomas, the loss of TUBB3 expression serves as a distinguishing molecular feature [89,90]. Regulation of TUBB3 in CNS tumors often involves developmental transcription factors such as SOX11 [91]. Overall, in CNS tumors TUBB3 expression is tightly linked to microtubule remodeling and reflects neuronal lineage dysregulation.

(2) Head and Neck Tumors

In papillary thyroid carcinoma, TUBB3 overexpression correlates with invasive behavior and poor prognosis [92,93]. For example, the TUBB3_38175 transcript, which includes alternative splicing involving exon 6, has been associated with invasive potential and may serve as a biomarker for distinguishing histological and molecular subtypes of thyroid cancer [94]. Similarly, in oral squamous cell carcinoma and nasopharyngeal carcinoma, aberrant TUBB3 expression is linked to tumor aggressiveness and altered tubulin polymerization [95,96]. Collectively, in head and neck tumors TUBB3 expression serves as a marker of tumor progression and diagnostic differentiation, with a strong association with invasion and metastasis.

(3) Digestive System Tumors

Aberrant expression of TUBB3 is frequent in gastrointestinal cancers, including esophageal, gastric, colorectal, and hepatic malignancies [97–100]. In gastric and esophageal cancers, high TUBB3 levels predict poor prognosis and resistance to taxane-based chemotherapy [97,98,101]. In colorectal cancer, TUBB3 interacts with non-coding RNAs to promote EMT, metastasis, and immune modulation [98,99,102]. TUBB3 is also implicated in HBx-induced hepatocarcinogenesis and functions as a novel marker in cholangiocarcinoma [100,103]. Taken together, in digestive system tumors TUBB3 supports malignant traits through the regulation of EMT, stemness, and interactions with the tumor immune microenvironment.

(4) Respiratory System Tumors

In lung cancers, including non-small cell lung cancer (NSCLC) and small cell lung cancer, TUBB3 overexpression has been consistently linked to tumor aggressiveness and poor patient outcomes [104–107]. TUBB3 is transcriptionally regulated by KRAS proto-oncogene, GTPase (KRAS) mutations and enhances tumor survival through the phosphatase and tensin homolog (PTEN)/AKT axis [105,107]. Moreover, its expression alters glucose metabolism and facilitates resistance to stress [104], while TUBB3 inhibition sensitizes lung cancer cells to immunotherapy [106]. Thus, in respiratory malignancies, TUBB3 functions as both a prognostic marker and a potential therapeutic target that bridges oncogenic signaling and metabolic adaptation.

(5) Urogenital Tumors

TUBB3 overexpression has been documented in renal cell carcinoma, bladder cancer, and prostate cancer, where it correlates with aggressive features, cancer stem cell markers, and poor survival [108–112]. Loss of p53 function is associated with TUBB3 upregulation in renal carcinoma [108], while aldehyde dehydrogenase 1 family member A1 (ALDH1A1) enhances retinoic acid biosynthesis to activate retinoic acid transcriptional signaling, which further drives TUBB3 overexpression to facilitate malignant proliferation and progression in bladder cancer [113,114]. In prostate cancer, TUBB3 expression is associated with both castration resistance and docetaxel resistance. Mechanistically, TUBB3-induced alterations in microtubule dynamics are thought to facilitate androgen receptor (AR) nuclear translocation—a microtubule-dependent process mediated by dynein motors - thereby sustaining AR transcriptional activity under androgen-depleted conditions and contributing to the emergence of

castration-resistant prostate cancer (CRPC) [115–117]. Overall, in urogenital tumors, TUBB3 expression reflects a convergence of stemness, genetic instability, and therapy resistance.

Overall, TUBB3 expression demonstrates both universal and context-specific roles in tumor biology [117]. Across diverse tumor types, TUBB3 dysregulation reflects a convergent, stress-adaptive cytoskeletal reprogramming program—driven by shared transcriptional/epigenetic and post-transcriptional mechanisms, coupled to EMT and stemness, encoded through isoform switching, and wired into pro-survival signaling networks—to promote chemoresistance and malignant progression. Elevated expression generally marks aggressive disease, particularly in digestive, respiratory, and urogenital cancers, whereas loss of expression can be diagnostically relevant in certain hematologic malignancies [12]. The heterogeneous prognostic implications underscore the “double-edged” role of TUBB3: it may either promote tumor aggressiveness or, in selected contexts, mark differentiation-associated favorable outcomes. Its clinical significance entirely depends on: tumor lineage, microenvironmental stress, treatment types, and their upstream regulatory background. This complexity highlights the need to interpret TUBB3 expression within the tissue-specific signaling environment and therapeutic background rather than as a uniform biomarker.

4.2. Physiological versus pathological roles of TUBB3

TUBB3 is expressed at low levels in most somatic tissues but is enriched in neurons and testicular germ cells, where it fulfills specialized physiological functions [25]. In the nervous system, TUBB3 supports axonal guidance, synaptic plasticity, and intracellular trafficking by modulating microtubule dynamics and interactions with motor proteins [17]. In germ cells, it contributes to meiotic spindle assembly and gametogenesis [118]. These contexts highlight TUBB3’s role in maintaining cellular polarity, motility, and differentiation under tightly regulated developmental programs.

In contrast, tumor cells frequently exploit TUBB3 in ways that deviate from its physiological role. Aberrant overexpression or dysregulated splicing of TUBB3 enhances microtubule stability in proliferating cancer cells, conferring survival under mitotic stress [94,117]. Post-translational modifications and oncogenic transcriptional programs rewire its regulation, coupling TUBB3 expression to EMT, stemness, and hypoxia adaptation [28]. Neuronal TUBB3 sustains constitutive axonal structural stability via balanced microtubule turnover, whereas tumor-derived TUBB3 rewires microtubule dynamics to facilitate acute cellular adaptation to cytotoxic and therapeutic stress [119].

From a therapeutic perspective, these differences reveal tumor-specific vulnerabilities. While physiological TUBB3 expression is most enriched in the nervous system and detectable in reproductive tissues such as the testis, its presence in other normal tissues is generally low but can be induced by oxidative stress, hypoxia/ischemia, and genotoxic stress via distinct transcriptional mechanisms [120–122]. In contrast, aberrant induction of TUBB3 in epithelial tumors has been consistently associated with increased aggressiveness, poor prognosis, and resistance to microtubule-targeting agents, particularly taxanes [9,12]. Notably, this resistance phenotype is largely driven by cancer-associated stress-responsive regulatory pathways, such as hypoxia, that are less active in normal differentiated tissues [12,123,124]. This divergence suggests that selectively targeting the oncogenic regulatory networks governing TUBB3 may reduce adverse effects on essential neuronal functions. Accordingly, TUBB3 has emerged as both a clinically relevant prognostic biomarker and a promising therapeutic target in oncology.

4.3. Regulation of TUBB3 and its implications in drug resistance

Aberrant expression of TUBB3 in malignant tumors is governed by complex regulatory networks involving transcriptional control, post-transcriptional modifications, and signal transduction pathways. Importantly, these same mechanisms underlie the ability of TUBB3 to mediate resistance to chemotherapeutic and targeted agents, emphasizing the interdependence between regulation and drug response.

(1) Post-translational and Epigenetic Regulation

TUBB3 undergoes diverse post-translational modifications that influence its stability, localization, and microtubule dynamics (Figure 4a). Phosphorylation by kinases such as DYRK1A, CDK1, and SRC proto-oncogene, non-receptor tyrosine kinase (SRC) regulates spindle assembly and mitotic progression [49,119,125], while acetylation at K252 reduces tubulin incorporation into MTs [27]. Phosphorylation and glycosylation states have also been correlated with cytoskeletal compartmentalization and resistance phenotypes [126]. Epigenetic mechanisms, including DNA methylation and histone acetylation, further modulate TUBB3 transcription in ovarian and other cancers [10,127]. These modifications collectively endow tumor cells with the ability to dynamically adapt microtubule architecture in response to therapeutic stress.

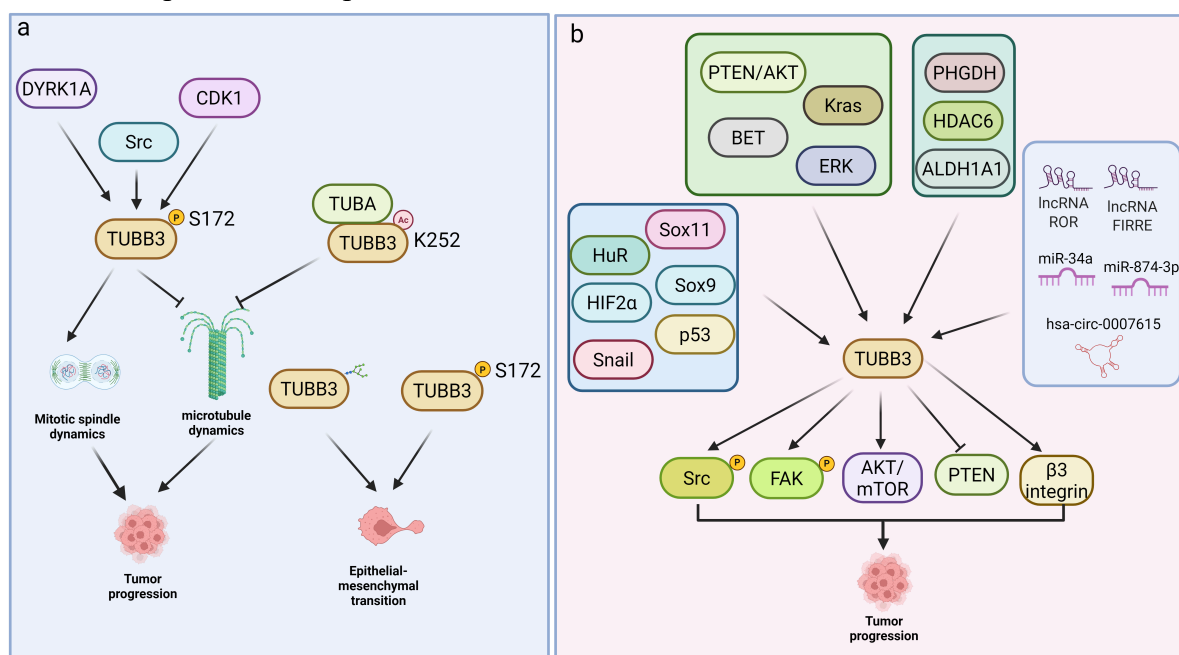


Figure 4. Post-translational modifications and signaling regulation of TUBB3 in cancer. **(a)** Post-translational modifications of TUBB3 and their functional implications. Key modifications include phosphorylation (Ser172, Ser339, Ser444), acetylation (K252), and glycosylation (Asn316), which modulate microtubule dynamics, drug sensitivity, and subcellular localization; **(b)** Signaling pathways regulating TUBB3 expression in cancer. Upstream regulators include PI3K/AKT/PTEN, MAPK/ERK, and transcription factors such as SOX9, HIF-2α, Snail, and p53. Non-coding RNAs (miR-200c, miR-34a, lncRNA FIRRE) provide additional layers of regulation.

(2) Signaling Pathways Governing TUBB3 Expression

Numerous oncogenic pathways converge on TUBB3 regulation (Figure 4b). The PI3K/AKT/PTEN axis plays a central role, where loss of PTEN or activation of AKT leads to TUBB3 upregulation and

enhanced survival under drug pressure [128–132]. Similarly, the MAPK/ERK pathway contributes to TUBB3-driven tumor proliferation and apoptosis resistance [129,133]. Transcriptional regulators such as SOX9, HIF-2 α , Snail, and p53 directly or indirectly affect TUBB3 expression, linking it to processes like EMT and stemness [108,122,126]. Non-coding RNAs, including miR-200c, miR-34a, lncRNA functional intergenic repeating RNA element (FIRRE), and circRNAs, provide additional layers of fine-tuned control [92,98,134–136]. Together, these mechanisms position TUBB3 at the intersection of multiple oncogenic networks.

(3) Mechanistic Basis of TUBB3-Mediated Drug Resistance

The same pathways that regulate TUBB3 expression also contribute to drug resistance (Figure 5). TUBB3 alters microtubule stability, thereby reducing the binding and efficacy of taxanes and vinca alkaloids [137–139]. In addition, its interaction with AKT and glucose-regulated protein 78 (GRP78) enhances survival signaling under nutrient deprivation or therapeutic stress [104]. Crosstalk with specific ABC transporters, particularly ABCB1 (P-glycoprotein), and DNA repair machinery contributes to multidrug cross-resistance [140,141]. TUBB3 thus operates as a central hub that integrates cytoskeletal remodeling with stress adaptation, explaining its consistent association with poor therapeutic response.

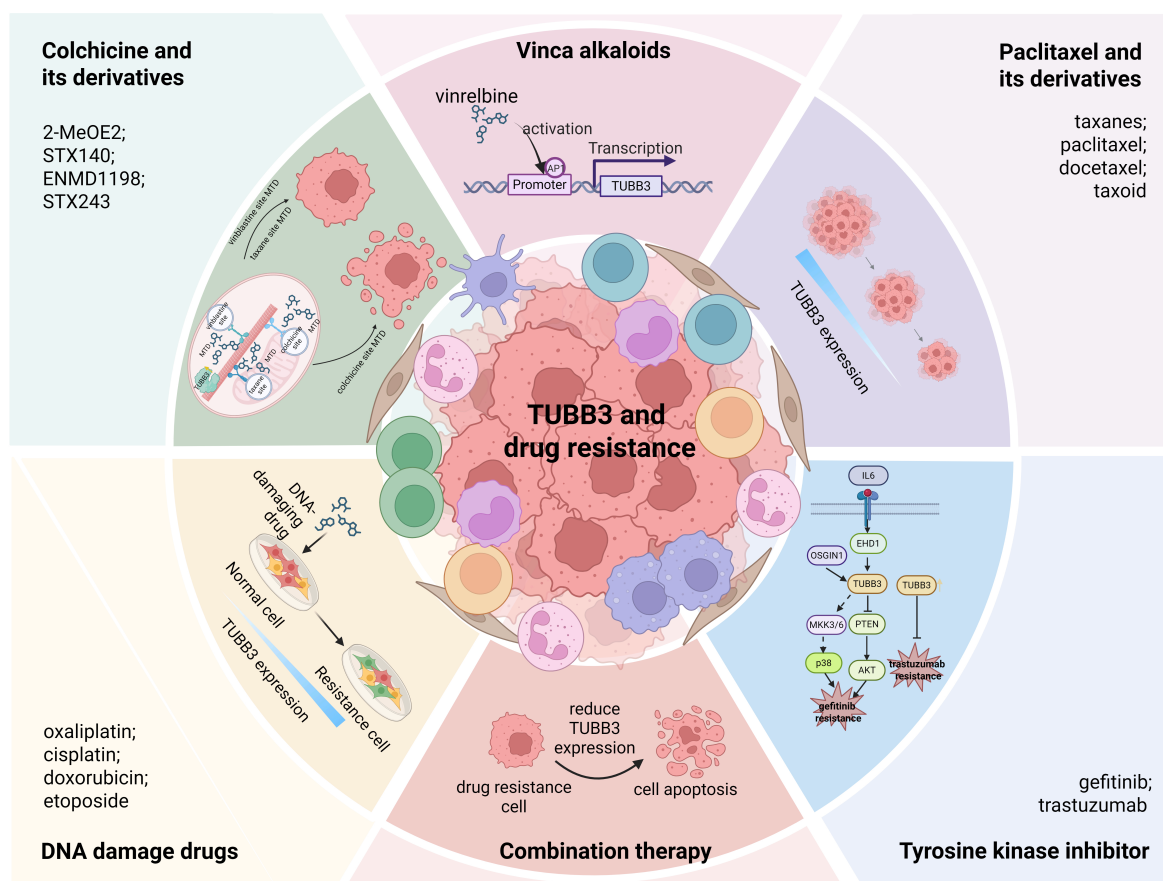


Figure 5. Role of TUBB3 in tumor-targeting drug resistance. TUBB3 overexpression contributes to resistance against multiple drug classes, including microtubule-targeting agents (taxanes, vinca alkaloids), DNA-damaging agents (platinum derivatives), and tyrosine kinase inhibitors (gefitinib). Mechanistically, TUBB3 alters microtubule dynamics, activates PI3K/AKT and MAPK/ERK survival signaling, and interacts with ABC transporters (ABCB1) and DNA repair machinery, thereby establishing a multidrug-resistant phenotype.

(4) Crosstalk Between TUBB3, Cell Cycle Regulation, and DNA Repair Pathways

Evidence indicates that TUBB3 contributes to chemoresistance through coordinated modulation of MT dynamics, cell-cycle checkpoints, and DNA repair [142–144]. Aberrant TUBB3 expression remodels MT dynamic instability and alters kinetochore attachment–detachment kinetics, thereby diminishing spindle assembly checkpoint (SAC) fidelity [142]. This perturbation is associated with shifts in the activation threshold of the anaphase-promoting complex/cyclosome (APC/C), predisposing cells to either premature mitotic exit (slippage) or prolonged arrest—both compatible with chromosomal instability and tolerance to cytotoxic stress. These SAC defects offer a structural rationale for the frequently observed, paradoxical attenuation of response to taxanes and vinca alkaloids in TUBB3-overexpressing tumors, despite these drugs' intended stabilization or depolymerization of MTs [145–147]. Beyond structural effects, TUBB3 frequently aligns with pro-proliferative signaling that facilitates checkpoint adaptation: in lung and ovarian carcinomas, higher TUBB3 levels correlate with PI3K/AKT activation, stabilization of Cyclin D1/cyclin-dependent kinase 4 (CDK4) and Cyclin B1/CDK1 complexes, and repression of p21^{Cip1}/p27^{Kip1} [105]. This cytoskeleton–signaling coupling plausibly accelerates G1/S and G2/M transitions, supports mitotic recovery under MT stress, and dampens apoptosis. Collectively, these data support a model in which TUBB3 biases the balance between MT stability and checkpoint restraint, favoring continued proliferation and reduced susceptibility to spindle poisons.

MTs also participate in genome maintenance by coordinating the spatial logistics of the DNA-damage response (DDR) [144]. Following genotoxic stress, activation of the DNA-dependent protein kinase (DNA-PK) (DNA-PK)–AKT axis increases MT turnover and centrosomal activity, thereby facilitating trafficking and assembly of repair complexes—in particular the BRCA1–PALB2–BRCA2–RAD51 machinery—at sites of double-strand breaks [143,148,149]. In TUBB3-high cells, microtubule remodeling is amplified, which is associated with increased homologous recombination (HR) focus formation and enhanced DNA lesion processing [144]. Concomitantly, AKT-dependent signaling associated with TUBB3 can sustain checkpoint kinase 1 (CHK1) phosphorylation and attenuate p53-mediated apoptosis, enabling checkpoint recovery despite residual damage [150,151]. Through this dual influence on temporal (checkpoint) and spatial (repair logistics) dimensions of the DDR, TUBB3 links cytoskeletal plasticity to genome maintenance, a combination that aligns with phenotypes of high proliferative capacity, genomic plasticity, and treatment tolerance [144,152].

In aggregate, current evidence supports TUBB3 as an integrator of MT dynamics, checkpoint control, and DNA-repair fidelity. By promoting checkpoint adaptation and expediting repair-complex mobilization, TUBB3 helps establish a state optimized for survival under cytotoxic pressure—providing a coherent mechanistic basis for attenuated responses to both microtubule-targeting and DNA-damaging agents. Nonetheless, the strength of these relationships varies across histologies, genetic backgrounds, and treatment contexts, underscoring the need for standardized functional assays and prospective validation when leveraging TUBB3 as a biomarker or therapeutic entry point.

4.4. Drug classes affected by TUBB3 expression

(1) Microtubule-Targeting Agents

Taxanes such as paclitaxel and docetaxel are directly impacted by TUBB3 expression. High TUBB3 levels predict reduced sensitivity in lung, gastric, and prostate cancers. Conversely, downregulation of TUBB3 re-sensitizes resistant cells to these agents [48,145,153,154]. Vinca alkaloids also exhibit reduced

efficacy in the presence of high TUBB3, although some studies report predictive value of combined TUBB3/ERCC1 immunoprofiles [13,155,156]. Interestingly, colchicine-binding site agents retain activity in TUBB3-overexpressing tumors, suggesting drug-site selectivity in resistance mechanisms [12,146].

(2) DNA-Damaging Agents

TUBB3 expression has been linked to reduced sensitivity to platinum derivatives such as cisplatin and oxaliplatin. Knockdown of TUBB3 enhances apoptosis and reverses resistance in colorectal and lung cancer models [48,157,158]. Thus, TUBB3 may act as a predictive marker for platinum-based chemotherapy outcomes.

(3) Tyrosine Kinase Inhibitors

In NSCLC, TUBB3 contributes to gefitinib resistance through modulation of PI3K/AKT and MAPK signaling [107,119,159]. Regulators such as oxidative stress induced growth inhibitor 1 (OSGIN1) enhance TUBB3-driven resistance via the mitogen-activated protein kinase kinase 3 (MKK3)/6-p38 pathway [119]. Targeting the IL-1 β /EH domain containing 1 (EHD1)/TUBB3 axis has been shown to overcome epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) resistance, highlighting the therapeutic value of pathway-directed interventions [107]. Notably, most existing mechanistic studies between TUBB3 and TKIs center on gefitinib; available data concerning osimertinib and crizotinib remain limited and inconsistent across cohorts, with no unified regulatory axis linking TUBB3 to their drug resistance phenotypes reported to date.

(4) Combination Therapies

Strategies combining TUBB3 inhibition with chemotherapy or immunotherapy have demonstrated preclinical efficacy [160]. Nanoparticle-mediated delivery of TUBB3 siRNA or miR-200c restores taxane sensitivity [161], while co-inhibition of TUBB3 and PI3K/AKT pathways synergistically enhances tumor cell apoptosis. Natural compounds and traditional medicine formulations have also been reported to reverse multidrug resistance by downregulating TUBB3 expression [162].

Taken together, the regulation of TUBB3 and its role in drug resistance represent a continuum rather than separate processes. Aberrant activation of oncogenic signaling drives TUBB3 expression, which in turn stabilizes MTs, reprograms cell survival, and establishes drug-resistant phenotypes. This reciprocal relationship positions TUBB3 as both a readout of oncogenic stress adaptation and a functional mediator of therapeutic failure. Clinically, the assessment of TUBB3 levels may therefore inform not only prognosis but also the rational design of combination therapies aimed at overcoming resistance.

5. Pharmacological targeting strategies against TUBB3

Due to the aberrant high expression of TUBB3 in many cancers and its prognostic effect, the development of TUBB3 targeted therapy is also a research area that researchers have been paying attention to. Clinical investigations involving β III-tubulin (TUBB3) have primarily evaluated its role as a predictive and prognostic biomarker rather than a direct therapeutic target; across multiple phase II–III trials, high TUBB3 expression consistently correlates with taxane resistance and poor clinical outcomes, while epothilone-class agents such as ixabepilone and patupilone show retained activity in TUBB3-high tumors, highlighting its translational relevance in optimizing microtubule-targeted therapy selection [130,145,153,163] (Table 1). These results suggested that high expression of TUBB3 correlated to poor prognosis. Due to the high homology of TUBB3 with other β -tubulin isotypes, it is difficult to develop small molecule inhibitors targeting this protein. Given the high expression of TUBB3 in cancer, strategies to silence TUBB3 have been

explored. At present, the main targeted therapeutic measures for TUBB3 involve small molecule inhibitors, microRNAs, signal transduction regulation and other research directions.

Table 1. Clinical studies involving TUBB3: interventions, disease context, mechanism/relation to TUBB3, development stage and key references.

Interventions	Target(s)	Disease Context(s)	Mechanism/Relation to TUBB3	Development Stage	Clinical Trial Registry	Registration Date	Reference
gemcitabine + cisplatin	TUBB3 ERCC1 RRM1	locally advanced breast cancer	The goal of the study is to investigate of the prognostics and predictive role of TUBB3 expression in locally advanced breast cancer.	Phase II	NCT06531447	2024-04	[164]
Ixabepilone	β -tubulin	Platinum-resistant or refractory ovarian/fallopian-tube/primary peritoneal cancer	Acts on β -tubulin microtubules; rationale includes ability to overcome taxane-resistance possibly mediated by high TUBB3 expression. Study explored TUBB3 as a predictive biomarker.	Phase II	NCT03093155	2017-03	[165]
Patupilone	β -tubulin	Advanced ovarian cancer (after platinum failure) and recurrent/progressive glioblastoma (GBM)	Epothilone class may retain activity in TUBB3-high tumours; trial included tubulin-inhibitor in settings of high TUBB3 expression.	Phase I/II	NCT00715013	2008-07	[166]
Taxane-based regimens (e.g., paclitaxel or docetaxel + cisplatin)	β -tubulin	Recurrent and metastatic gastric adenocarcinoma	High TUBB3 expression associated with shorter PFS on taxane-based chemotherapy; hence TUBB3 studied as predictive marker of taxane response.	Retrospective study	Not applicable	Not applicable	[145]
Gemcitabine + cisplatin vs. paclitaxel + carboplatin (IFCT-0002)	Gemcitabine: antimetabolite; Cisplatin/Carboplatin: DNA cross-linking agents; Paclitaxel: microtubule stabiliser (β -tubulin)	Resectable stage I–II NSCLC, preoperative (neoadjuvant) chemotherapy	High TUBB3 expression was evaluated as a predictive and prognostic marker for response and survival after taxane- or gemcitabine-based regimens; high TUBB3 was associated with poorer outcome and linked to KRAS signalling.	Exploratory study	IFCT-0002 (French intergroup)	Not applicable	[130]

Table 1. *Cont.*

Interventions	Target(s)	Disease Context(s)	Mechanism/Relation to TUBB3	Development Stage	Clinical Trial Registry	Registration Date	Reference
FOLFIRI → docetaxel + cisplatin vs. 5-FU/leucovorin (5-FU/LV) (ITACA-S; NCT01640782)	Irinotecan: topoisomerase I inhibitor; Docetaxel: microtubule stabiliser (β -tubulin); Cisplatin: DNA cross-linker; 5-FU/LV: fluoropyrimidine antimetabolite	Radically resected gastric cancer (adenocarcinoma of the stomach/GEJ) receiving adjuvant chemotherapy	High TUBB3 was explored as a negative predictive biomarker of benefit from docetaxel-based taxane therapy: patients with high TUBB3 tended to have worse OS on docetaxel-based regimen vs. 5-FU/LV, with a significant treatment–TUBB3 interaction.	Phase III	NCT01640782	2005-02	[167]
S-1 (oral fluoropyrimidine) vs. taxane (paclitaxel or docetaxel)–SELECT-BC	S-1: prodrug combination of 5-FU (tegafur + modulators); Taxanes: microtubule stabilisers (β -tubulin)	HER2-negative, hormone-therapy-resistant metastatic breast cancer, first-line chemotherapy	TUBB3 may act as predictive markers for S-1 efficacy	Phase III	UMIN-CTR:C000000416	2006-10	[168]
Neoadjuvant doxorubicin/cyclophosphamide (AC) → ixabepilone vs. paclitaxel	Ixabepilone: microtubule stabilizer (epothilone B analogue, β -tubulin binding); Paclitaxel: taxane microtubule stabilizer	Early-stage, operable breast cancer (stage II–III)	Evaluate β III-tubulin (TUBB3) expression by IHC as a predictive biomarker for response to ixabepilone vs. paclitaxel following AC; microtubule-targeted therapy after anthracycline-based induction	Phase II	NCT00455533	2007-10	[169]

5.1. Small-molecule inhibitor–based strategies

Small-molecule inhibitors constitute a major class of therapeutic agents due to their favorable pharmacological properties. Several compounds have been reported to modulate TUBB3 either directly or indirectly (Table 2). Drugs like Paclitaxel, Nocodazole, Eribulin, Combretastatin A4, VERU-111, PMMB276, Ixabepilone and Gambogic acid target tubulin directly, either by stabilizing or destabilizing microtubules, which disrupts mitosis and leads to cancer cell death. Some of these agents also specifically inhibit the expression or activity of TUBB3 [170–174].

Indirect modulation of TUBB3 has also been achieved through inhibitors of upstream regulators. For example, the histone methyltransferase inhibitor BIX01294 suppresses TUBB3 expression in glioma [175], while the PI3K inhibitor LY294002 re-sensitizes taxane-resistant cells by downregulating TUBB3 [137]. Similarly, inhibition of P2RX7 (via KN62) prevents LL-37–induced TUBB3 upregulation and restores sensitivity in colon cancer models [176]. Collectively, these data highlight the therapeutic versatility of small molecules in modulating TUBB3 expression and activity.

Table 2. Inhibitors involving TUBB3: molecular structural formula, target(s), disease context, mechanism/relation to TUBB3, development stage and key references.

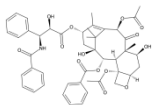
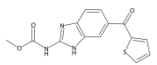
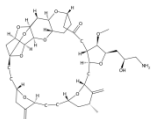
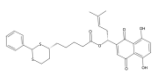
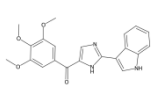
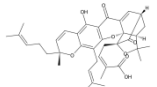
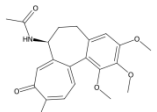
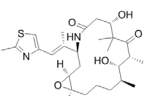
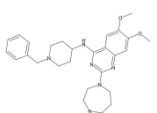
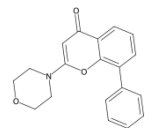
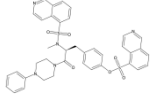
Type	Agent	Molecular structural formula	Target(s)	Disease Context(s)	Mechanism/Relation to TUBB3	Reference
Direct inhibitors	Paclitaxel		α/β -tubulin heterodimers (including TUBB3)	Including Breast cancer, ovarian cancer, non-small cell lung cancer, head and neck cancer.	By binding to β -tubulin, it stabilizes microtubules and prevents their depolymerization. This leads to cell arrest in the G2/M phase and triggers apoptosis.	[177]
	Nocodazole		α/β -tubulin heterodimers (including TUBB3)	Including colorectal cancer.	By binding to β -tubulin, it inhibits microtubule polymerization, causing microtubules to disassemble, resulting in the cessation of mitosis and ultimately leading to cell death.	[171]
	Eribulin		α/β -tubulin heterodimers (including TUBB3)	Metastatic breast cancer, head and neck squamous cell carcinoma (HNSCC)	Binds β -tubulin, suppresses microtubule growth ("end-poisoning"), causes mitotic arrest; in HNSCC, eribulin reduced TUBB3 expression correlating with antiproliferative activity.	[170]
	Combretastatin A4		α/β -tubulin heterodimers (including TUBB3)	Including Colon cancer, lung cancer, leukemia.	Combretastatin A4 directly binds to the colchicine-binding site of tubulin (β -tubulin), thereby inhibiting microtubule polymerization or promoting its depolymerization.	[172]
	PMMB276		TUBB3	breast cancer	binds TUBB3, induces microtubule depolymerisation, cell cycle arrest (G2/M), apoptosis in TNBC in vitro and in vivo.	[178]
	VERU-111		α/β -tubulin heterodimers (colchicine-binding site), preferential β III & β IV isoforms	Pancreatic cancer, ovarian cancer, triple-negative breast cancer, taxane-resistant solid tumours	Orally bioavailable tubulin polymerization inhibitor. Binds the colchicine site of tubulin, preferentially suppresses β III-tubulin and β IV-tubulin expression (via restoring miR-200c) in pancreatic cancer models, arrests cells in G2/M, induces apoptosis, inhibits migration/invasion and metastasis.	[173,179]

Table 2. *Cont.*

Type	Agent	Molecular structural formula	Target(s)	Disease Context(s)	Mechanism/Relation to TUBB3	Reference
	Gambogic acid		TUBB3, survival proteins	Various cancers (combined with docetaxel)	Natural product that downregulates TUBB3 expression when used in combination with docetaxel, resulting in synergistic antitumor effects.	[180]
	Colchicine		Tubulin (including TUBB3)	Gout, Cancer	Inhibits tubulin polymerization, causing microtubule destabilization and potentially affecting TUBB3 in cancer cells.	[181]
	Ixabepilone		Tubulin (including TUBB3)	breast cancer	Binding to tubulin (including TUBB3) promotes microtubule stabilization, leading to a blockage of mitosis.	[182]
Indirect modulators	BIX01294		Histone methyltransferase	Glioma	Inhibits histone methyltransferases, leading to suppression of TUBB3 expression in glioma cells.	[175]
	LY294002		PI3K	Taxane-resistant cancers (e.g., breast, prostate)	PI3K inhibitor that downregulates TUBB3 expression, resensitizing taxane-resistant cancer cells to treatment.	[137]
	KN62		P2RX7	Colon cancer	Inhibits P2RX7, preventing LL-37-induced upregulation of TUBB3 and restoring sensitivity to treatment in colon cancer models.	[176]

5.2. *siRNA and mRNA-based therapeutic approaches*

Direct silencing of TUBB3 transcripts has shown promise in reversing drug resistance. Several studies demonstrate that delivery of miR-200c—either alone or co-encapsulated with docetaxel in nanoparticles—enhances chemotherapy efficacy by repressing TUBB3 [183,184]. Similarly, miR-34a modulates microtubule stability through the STMN1/TUBB3 axis, leading to network disruption and apoptosis [135].

Beyond microRNAs, siRNA-based approaches have proven highly effective in preclinical settings. Both transient and stable TUBB3 knockdown strategies improve sensitivity to microtubule-targeting agents and suppress metastasis in NSCLC and pancreatic cancer models [48,185,186]. Advanced delivery systems, including polymerized star nanoparticles and lipid-based carriers, have successfully transported TUBB3-siRNA to in vivo tumor sites, significantly reducing tumor burden and enhancing taxane efficacy [187–190]. These approaches establish RNA-based therapeutics as a potent avenue for targeting TUBB3-driven resistance.

5.3. *Targeting TUBB3 regulatory networks*

Given the complex upstream signaling that governs TUBB3 expression, modulation of these pathways provides alternative therapeutic entry points. K-Ras knockdown decreases TUBB3 expression in bronchial cells, suggesting potential for combining anti-mitogen-activated protein kinase kinase (anti-MEK) or anti-PI3K agents with standard chemotherapy in TUBB3-overexpressing tumors [130]. Similarly, ALDH1A1 suppression reduces TUBB3 expression, opening possibilities for biomarker-driven interventions in advanced disease [114].

Inhibition of PTEN/AKT axis diminishes TUBB3 and DNA topoisomerase II alpha (TOP2A) expression, curtailing growth and inducing apoptosis via caspase-3 activation in breast cancer cells [128]. Interestingly, bromodomain and extraterminal domain (BET) inhibition paradoxically upregulates TUBB3 but sensitizes metastatic breast cancer to vinorelbine, underscoring the complexity of network-level interactions [191]. Additionally, regulators such as Rab interacting lysosomal protein like 2 (RILPL2) modulate docetaxel response through TUBB3/PTEN/AKT signaling [192]. Natural compounds also provide novel opportunities; for instance, the marine bacterial polysaccharide Exopolysaccharide 11 (EPS11) downregulates TUBB3 at both transcriptional and translational levels, exerting anti-cancer effects [132].

Taken together, therapeutic approaches directed at TUBB3 can be broadly categorized into small-molecule inhibitors, RNA-based therapeutics, and pathway-targeted interventions. Each strategy has demonstrated the capacity to reduce TUBB3 expression, resensitize resistant cells, and enhance the efficacy of conventional chemotherapy in preclinical models. However, evidence also indicates that no single intervention is sufficient to fully abrogate TUBB3-mediated resistance, largely due to compensatory signaling and the structural redundancy inherent to the tubulin family. In this context, combination therapies—such as co-delivery of TUBB3-silencing constructs with taxanes, or simultaneous inhibition of PI3K/AKT signaling and TUBB3—have shown superior efficacy compared to monotherapies. Moreover, the incorporation of patient stratification based on TUBB3 expression and related biomarkers may allow for more rational therapeutic design, ensuring both effectiveness and minimized systemic toxicity. This integrated perspective underscores the need to contextualize TUBB3 within the broader β -tubulin isoform family, where functional overlaps and divergences may further shape therapeutic outcomes.

6. Conclusions and future perspectives

Aberrant regulation of TUBB3 represents a crucial determinant of cancer biology, bridging microtubule remodeling with oncogenic signaling, metabolic adaptation, and therapeutic resistance. TUBB3's context-dependent functions across cytoskeletal remodeling, oncogenic signaling networks, and therapy-resistance programs to reveal how this neuron-specific tubulin isoform is repurposed by cancer cells as a central mediator of malignant plasticity and treatment failure. Accumulating evidence shows that TUBB3 is dysregulated at multiple levels, including genetic mutations, post-translational modifications, and aberrant transcriptional or post-transcriptional control. These alterations converge on a limited number of cancer-relevant pathways such as PI3K/AKT, MAPK/ERK, and EMT-associated programs, thereby enabling tumor cells to adapt to cytotoxic stress and acquire multidrug resistance. Importantly, the clinical implications of TUBB3 extend beyond its role as a passive biomarker: it acts as a functional driver of chemoresistance, survival under hypoxia, and metastatic progression. The context-dependent nature of TUBB3—serving as a neuronal differentiation marker under physiological conditions but as a stress-responsive isoform in malignant tissues—underscores its unique position as both a diagnostic challenge and a therapeutic opportunity.

From a translational standpoint, multiple therapeutic avenues have been explored, including small-molecule modulators, RNA-based strategies, and indirect targeting via upstream signaling pathways. Preclinical studies demonstrate that silencing TUBB3 or restoring its regulatory non-coding RNAs can resensitize resistant tumors to taxanes and platinum agents, while VERU-111, an agent preferentially suppressing oncogenic TUBB3 and TUBB4 isoforms with minimal activity against other β -tubulins, validates isoform-biased pharmacological targeting of tubulin-mediated chemoresistance [179]. Nonetheless, the high sequence homology across β -tubulin isoforms, compensatory interactions with TUBB2A or TUBB4, and the dual physiological–pathological functions of TUBB3 remain formidable obstacles. Furthermore, clinical studies investigating TUBB3 expression as a predictive biomarker have produced variable results depending on cancer type and therapeutic context, indicating the urgent need for standardized assays and multi-marker predictive panels.

Looking forward, future research should prioritize integrative, multi-omics approaches to dissect the context-specific mechanisms of TUBB3 dysregulation and their interplay with the broader tubulin network. Advances in single-cell and spatial transcriptomics, clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR–Cas9)-based functional screening, and next-generation RNA therapeutics will be instrumental in refining TUBB3 as a precision oncology target. Equally important is the careful stratification of patients based on TUBB3 expression and associated regulatory networks to optimize therapeutic outcomes while minimizing off-target effects in neuronal and reproductive tissues. By moving beyond descriptive associations toward mechanistic and translational integration, TUBB3 can be transformed from a marker of therapeutic failure into a strategic vulnerability in cancer, offering new opportunities for precision medicine and individualized treatment design.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. Specifically, the authors used ChatGPT for language polishing only. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Conceptualization, X.X., X.T., D.J.K. and Z.D.; writing—original draft preparation, X.X.; writing—review and editing, X.X., X.T., D.J.K. and Z.D.; visualization, X.L., D.Z. and X.W. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

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