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ANTI-TUMOUR TREATMENT

Microtubule dynamics as a target in oncology

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SUMMARY

Drugs that affect microtubule dynamics, including the taxanes and vinca alkaloids, have been a mainstay in the treatment of leukemias and solid tumors for decades. New, more effective microtubule-targeting agents continue to enter into clinical trials and some, including the epothilone ixapebilone, have been approved for use. In contrast, several other drugs of this class with promising preclinical data were later shown to be ineffective or intolerable in animal models or clinical trials. In this review, we discuss the molecular mechanisms as well as preclinical and clinical results for a variety of microtubule-targeting agents in various stages of development. We also offer a frank discussion of which microtubule-targeting agents are amenable to further development based on their availability, efficacy and toxic profile.

Microtubule structure and dynamics

Microtubules are dynamic structures that are required for a variety of cellular processes. Microtubules, along with actin microfilaments and intermediate filaments, form the cytoskeleton. The highly organized arrangement of microtubules is required for intracellular trafficking of vesicles and organelles, cellular motility and mitotic chromosome segregation. Actin microfilaments also play an important role in mitosis, as they are required for cellular cleavage during cytokinesis.

Microtubules are formed by the association of α- and β-tubulin heterodimers that are folded and unfolded by chaperones as a heterodimer complex.[1] These heterodimers assemble head-to-tail into linear protofilaments that further polymerize to give rise to the characteristic hollow microtubule cylinder with internal and external diameters of 12 nm and 25 nm, respectively[2] (Fig. 1). This final structure is organized in a polar manner such that the α-tubulin subunit is exposed at one end (the minus end), while the β-tubulin subunit is exposed at the other (the plus end). GTP binding and hydrolysis on β-tubulin largely dictate the stability of the microtubule polymer at the more dynamic plus end. There are two GTP-binding sites on tubulin, a hydrolyzable site on the β-subunit and a non-hydrolyzable site on the α-subunit. The β-tubulin subunit must be bound to GTP at the hydrolyzable site for assembly into microtubules, shortly after which the GTP is irreversibly hydrolyzed to GDP. Thus, the majority of β-tubulin in the microtubule fiber is in the GDP-bound form and "capped" with GTP-bound β-tubulin at the plus end. When the GTP on a β-tubulin molecule is hydrolyzed to GDP before another GTP-bound β-tubulin is added, the exposed GDP-β-tubulin leads to a conformational change that results in rapid depolymerization of the microtubule in an event known as microtubule catastrophe. The relatively rapid lengthening and shortening at the microtubule plus end is referred to as dynamic instability. In contrast, a more controlled loss of tubulin subunits from the minus end and gain of tubulin subunits to the plus end with no net change in microtubule mass is termed treadmilling. Microtubule-associated proteins (MAPs) and microtubule-interacting drugs can promote or inhibit microtubule catastrophe as well as affect the rate of microtubule growth and shortening.[3]

Microtubule dynamics play a large role in the process of mitosis. During the majority of the cell cycle, microtubules form an intracellular lattice-like structure. However, when cells enter mitosis, this microtubule network is reorganized into the mitotic spindle. The processes of depolymerizing the interphase microtubule structure and forming the mitotic spindle, as well as finding,

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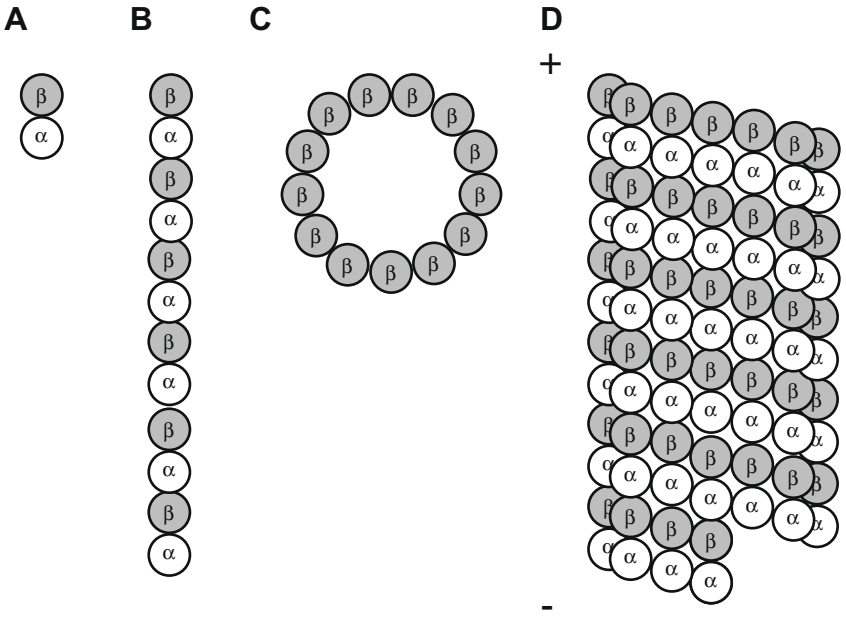

Figure 1. Microtubule structure. (A) Tubulin heterodimers are composed of α- and β-subunits that polymerize head-to-tail to form protofilaments. (B) Thirteen protofilaments form lateral contacts to create the hollow cylindrical structure of the microtubule (C and D) with β-tubulin exposed at the microtubule plus end (+) and α-tubulin exposed at the microtubule minus end (−).

attaching and separating chromosomes, require highly coordinated microtubule dynamics.[4] Therefore, agents that interfere with microtubule dynamics inhibit the ability of cells to successfully complete mitosis, thus limiting proliferation.

Drugs that inhibit microtubule dynamics have been used in the clinic as anticancer drugs for over 20 years. These drugs bind to tubulin, and at high concentrations cause an increase or decrease in the interphase microtubule mass. These compounds are classified as microtubule stabilizers or destabilizers, respectively (Fig. 2). However, it has been shown that at lower, clinically relevant concentrations, both classes of drugs inhibit mitosis through a similar mechanism of slowing microtubule dynamics, resulting in mitotic arrest and apoptosis.[5,6] Although microtubule-targeting agents have enjoyed great clinical success as chemotherapeutics, there remain significant downfalls to their use, including innate and acquired drug resistance. As a result, new agents that target microtubule dynamics are continually being sought out.

Microtubule destabilizers

Vinca site-binding agents

The vinca alkaloids, isolated from the periwinkle plant, *Catharanthus roseus*, are potent microtubule destabilizing agents that were first recognized for their myelosuppressive effects.[7] The original members of this family to undergo clinical development, vinblastine (Velban®) and vincristine (Oncovin®), were introduced into the clinic in the late 1950s. Second-generation semi-synthetic vinca analogs, including vindesine (Eldisine®), vinorelbine (Navelbine®) and vinflunine, have been developed and are used in the treatment of a variety of cancers.

The vinca alkaloids bind to β-tubulin near the GTP-binding site.[8,9] At low, clinically relevant concentrations, this binding occurs at the exposed microtubule plus end, resulting in decreased dynamics and mitotic arrest (Fig. 3).[10] Thus, the vincas are sometimes referred to as "end poisons". In contrast, the gross effect of microtubule destabilization is observed when sufficient drug is present to bind and disrupt tubulin interactions along the surface of the microtubule (Fig. 2). The vincas also have affinity to free tubulin heterodimers and can give rise to tubulin paracrystals at high concentrations.[11] While tubulin binding and suppression of microtubule dynamics are credited for the antineoplastic properties of the vinca alkaloids, these properties also lead to many of the observed side effects of these agents.

Although the structures of the various vinca alkaloids vary only slightly, they have distinct niches as chemotherapeutic agents. Vincristine is most effective in the curative treatment of leukemias, lymphomas and sarcomas. A liposomal sphingosomal vincristine

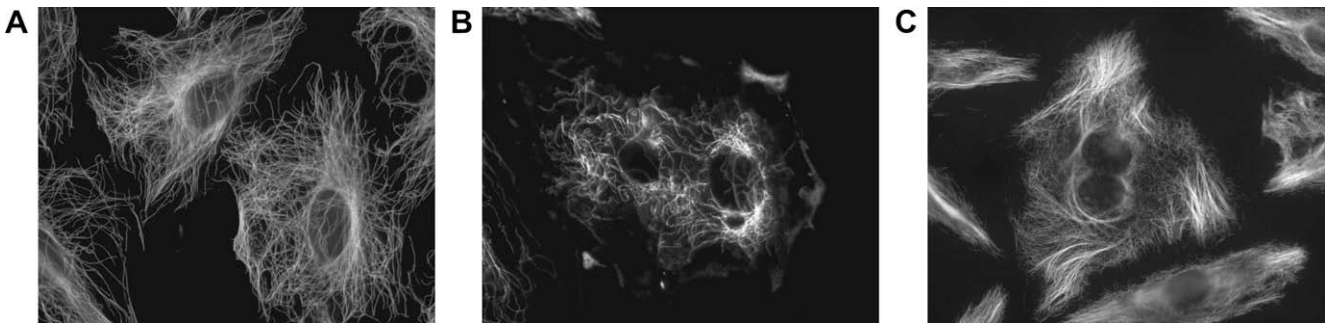

Figure 2. The effect of microtubule-targeting agents on interphase microtubules. A10 cells were treated with vehicle (A), 250 nm vinblastine (B), or 2 μm paclitaxel (C), for 18 h. Microtubules were visualized by indirect immunofluorescence using a β-tubulin antibody.