Recent Advances on Small-Molecule Tubulin Inhibitors

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Abstract Microtubules are heterodimers composed of α/β tubulin and make up the cytoskeleton. It plays an important role in maintaining cellular morphology, cell division, signal transduction and other processes. At present, six tubulin inhibitor binding sites have been identified. The inhibitors can be divided into two categories: a type of microtubule polymerization agent includes colchicine site, vinblastine site, maytansine site and prionetin site inhibitors; another category is paclitaxel and laulimalide/peloruside binding site inhibitors are called microtubule depolymerization. Herein, we summarize relevant inhibitors acting on these 6 sites and their research status. With extensive research on tubulin binding sites and inhibitors, anti-tumor tubulin inhibitors will possess very broad clinical prospects.

Keywords microtubule, tubulin, binding site, inhibitors

Introduction

Microtubules are of great importance for making up cytoskeleton and present in eucaryote cells. Tubulin is a protein family containing multiple members, and many types of tubulin such as α , β , γ , δ , ϵ , ζ and η have been discovered.^[1] Among them, α/β -tubulin account for 80%—95% of the amount of tubulin, and tubulin is a heterodimers structure with α/β -tubulin as the basic unit (Figure 1). Microtubules participate in various physiological functions of cells, including forming cytoskeleton, maintaining the cell pattern, taking part in material transportation, organelle transfer, making the movement of chromosomes. Tubulin synthesis is a dynamic process, including the polymerization process and depolymerization process of tubulin. Characteristics of this quick polymerization and depolymerization are called dynamics or dynamic instability of microtubules.

Figure 1 The basic structure of microtubules and tubulin.^[6]

Due to rapid multiplication of tumor cells, microtubules play an important role in the process of cellular mitosis, and then microtubules become one of the effective targets for antitumor drugs. In the process of cancer cell mitosis, microtubule inhibitors prevent the formation of spindles, resulting in abnormal chromosomes, arresting the cell cycle and promoting apoptosis.^[2,3] At present, six tubulin inhibitor binding sites

Figure 2 Six known binding sites on α -tubulin and β -tubulin.^[4]

(Figure 2) have been defined, namely paclitaxel binding site, laulimalide/peloruside A binding site, the colchicine binding site, Vinblastine binding site, maytansine binding site and prionetin binding site.^[4-6] According to different mode of action with tubulin, the inhibitors are divided into two categories. One is an inhibitor that binds to colchicine site, vinblastine site, maytansine site and prionetin site, which can inhibit polymerization of tubulin, promote depolymerization of microtubules; it is called microtubules depolymerization agent. Another inhibitor is to promote polymerization of tubulin to form microtubules and inhibit depolymerization of the formed microtubules, which is called microtubules polymerizer. These inhibitors can bind to paclitaxel site, laulimalide/peloruside A site. Herein, we summarized the inhibitors acting on six different binding sites of tubulin heterodimers and their research status.

Microtubules Depolymerization Agents

Colchicine binding site inhibitors

The colchicine site is located in the deep pocket of the middle region of the β -tubulin heterodimer. It is surrounded by β -tubulin on the helix H7, hoop H8, T7, chain S8, S9 and ring

T5 on α -tubulin. The inhibitor acting on this site includes colchicine, indoles, and podophyllotoxin. Colchicine is alkaloid, isolated from *saffron Colchicum autumnale* L. In cancer cells, it binds to tubulin dimers, hinders cell mitosis, and triggers cell apoptosis. Some studies have found that colchicine has an inhibitory effect on multiple cancer cells (MDA-MB231, A549 and HCT116) proliferation.^[7] The structure of ZD6126 is similar to that of colchicine and has potential anti-angiogenesis and anti-tumor activities. Due to its strong toxicity, the study was terminated in Phase II.^[8] Other multiple natural products and their analogs can also show effective anti-mitosis and anti-cancer activation by binding to colchicine sites. Combretastatin A-4 (CA-4) is isolated from the bark of the South African bush willow tree *Combretum caffrum*.^[9] AVE8062 is a derivation derivative of CA-4 containing amino groups and is currently in phase III clinical for the treatment of patient with later period solid tumors.^[10,11] Podophyllotoxin is a natural anti-tumor component compound of wood lipids extracted from *Podophyllum*, which can inhibit the assembly of microtubules cancer cells to treat gastric cancer cells.^[12] Curacin A can inhibit cell mitosis by binding to colchicine sites.^[13] The effect of chalcone analog MDL-27048 on microtubules is similar to that of colchicine.^[14] The sulfonamide analog ELR510444 can directly interact with tubulin through the colchicine binding site to destroy microtubule activity and effectively inhibit the proliferation of MDA-MB-435 cells.^[15] Some indole compounds can also inhibit polymerization of tubulin through the colchicine site binding to tubulin, thereby exerting effective anti-tumor and anti-mitotic activities, for example, BPR0L075,^[16] D-64131^[17] (Figure 3).

Vinca alkaloid binding site inhibitors

The Vinca alkaloid binding site is located on internal interface of tubulin dimer and consists of a core region and a pocket extending to the GTP on β -tubulin. Among them, the secondary structural units of the core region included helix H6, loop T5 and H6-H7 of β -tubulin, and helix H10, chain S9 and hoop T7 of α -tubulin.^[22] Vinblastine compounds and Halichondrin B and its derivatives can affect this site. Vinblastine is alkaloid with antitumor activity from *Catharanthus roseus*, inhibits the assembly of tubulin units into microtubules, resulting in the arrest of cell division in metaphase period.^[23] Halichondrin B is a large polyether macrocyclic lactone, which can be separated from the marine sponge *Halichondria okadai*. *In vitro* experiments proved that halichondrin B can non-competitive inhibit the binding of vinblastine to tubulin, and act on the vinblastine site to inhibit the polymerization of tubulin.^[24] E7389 is a synthetic derivative of halichondrin B, which can inhibit mitosis.^[25] Hemiasterlin A and hemiasterlin B are tripeptides isolated from marine sponges, which can prevent cell proliferation in the G2-M phase and act as antimetabolic agents.^[26] Dolastatin is a small peptide isolated from *Dolabella auricularia*, which can interact with tubulin and inhibit the growth of human ovarian and colon cancer cells (Figure 3).^[27]

Maytansine binding site inhibitors

The maytansine binding site is located on β -tubulin close to the GTP binding site, mainly composed of the hoop H10-S9, chain S8 and helix H8 of α -tubulin, the loop T3, T5, and H11-H12 of β -tubulin. Maytansine is a hilt macrocyclic lactones with anti-tumor effect. It interferes with microtubule formation by inhibiting polymerization of tubulin, thereby inhibiting mitosis.^[4] Some studies have found that PM060184 and rhizoxin have the

same active sites as maytansine, which also inhibits the formation of microtubules.^[28] In addition, polacbulin is a novel type of microtubule inhibitor destabilizing on the site of maytansine, and it has antitumor activity (Figure 3, Table 1).^[29]

Pironetin binding site inhibitors

Pironetin site is located on α -tubulin, which is mainly composed of helix H7 and chain S4, S5, S5, S8 and S10. Pironetin binds to α -tubulin and is an effective inhibitor of tubulin assembly. Some studies have found that in CDF1-SLC mice with leukaemia cells, peritoneal injection pironetin has an anti-tumor effect (Figure 3, Table 1).^[30]

Microtubules polymerizer agents

Taxane binding site inhibitors

The taxane binding site is located on the β -tubulin subunit on the inner surface microtubules lumen, which is mainly composed of β -tubulin helix H7, chain S7, loop H6-H7, M-loop and the hydrophobic residues of S9-S10. The main inhibitors acting on this are paclitaxel and its analogues, ebomycin and discodermolide. Paclitaxel is extracted from the bark of *Taxus brevifolia*, and it is a diterpenoid compound with a taxane ring.^[31] There is an interaction between microtubules and caspase 8, and this effect is enhanced after paclitaxel treatment, suggesting that paclitaxel may activate caspase 8 through microtubule to trigger apoptosis.^[32] Epothilones B reveal a similar mechanism of action as paclitaxel is bound to the β -tubulin, which can promote tubulin polymerization, thereby causing cell division to stop in mid-mitosis, and ultimately leading to tumor cell apoptosis.^[33] Discodermolide is an alkatetraene lactone, a microtubule stabilizer, and has an effect similar to epothilone (Figure 3, Table 1).^[34]

Laulimalide/peloruside A binding site inhibitors

Laulimalide/peloruside A is isolated from *Mycale hentscheli* and *Caccospongia mycofijiensis*, respectively (Figure 3, Table 1).^[35,36] They target the binding sites on β -tubulin to promoting the assembly of microtubules,^[37] stabilize microtubules, and induce mitosis arrest, which lead to cell death.

Conclusion and Perspective

At present, natural products and their analogues play an important role in tubulin inhibitors. Many compounds are in clinical or clinical trials (such as Paclitaxel, Vinorelbine, etc.). These inhibitors can inhibit tumor growth. However, some compounds have limited clinical application due to their toxicity and side effects. For example, the CA-4 inhibitor acting on the colchicine site is poorly water-soluble and metabolically unstable, and its clinical application is limited; vincristine that acts on the site of vinblastine limits its clinical application due to its toxicity and irritation. Therefore, there is still a lot of research space for tubulin inhibitors, and research on the structural modification of natural products is constantly being carried out and becoming more and more important.

Tubulin inhibitors are a wide range of anti-tumor drugs and play a key role in cancer treatment. Different types of anti-tubulin drugs can act on different binding sites and have good cytotoxicity. In summary, people have obtained a variety of microtubule activity inhibitors from many natural products, and modified the structure of some of them, so that these compounds have strong anti-tumor activity. Among them, the compounds and their analogues acting on the colchicine site have become a research hotspot in recent years and have

Figure 3 The chemical structures of small-molecule tubulin inhibitors.

Table 1 Binding constants of drugs that inhibit tubulin polymerization and polymerization

Binding sites	Compounds	Types	Binding constants	Ref.
Colchicine site	Colchicine	Tubulin polymerization	$3.31 \times 10^6 \text{ M}^{-1}$	[18]
	Combretastatin A-4	Tubulin polymerization	$1 \times 10^6 \text{ M}^{-1}$	[9]
	AVE8062	Tubulin polymerization	—	[10, 11]
	Podophyllotoxin	Tubulin polymerization	$1.8 \times 10^6 \text{ M}^{-1}$	[12]
	Curacin A	Tubulin polymerization	$3.2 \times 10^5 \text{ M}^{-1}$	[13]
	ZD6126	Tubulin polymerization	—	[8]
	BPR0L075	Tubulin polymerization	—	[16]
	D-64131	Tubulin polymerization	—	[17]
	ELR510444	Tubulin polymerization	—	[15]
	MDL-27048	Tubulin polymerization	—	[14]
Vinblastine site	Vinblastine	Tubulin polymerization	$3-4 \times 10^3 \text{ M}^{-1}$	[19, 23]
	Vinorelbine	Tubulin polymerization	$5.4 \times 10^6 \text{ M}^{-1}$	[20]
	Vincristine	Tubulin polymerization	$5.4 \times 10^6 \text{ M}^{-1}$	[20]
	Halichondrin B	Tubulin polymerization	—	[23, 24]
	Hemiasterlin	Tubulin polymerization	—	[26]
	Dolastatin	Tubulin polymerization	—	[27]
Maytansine site	Maytansine	Tubulin polymerization	—	[4]
	PM060184	Tubulin polymerization	—	[28]
Pironetin site	Pironetin	Tubulin polymerization	—	[30]
Taxane site	Paclitaxel	Tubulin polymerization	$1.43 \times 10^7 \text{ M}^{-1}$	[21]
	Docetaxel	Tubulin polymerization	$3.93 \times 10^7 \text{ M}^{-1}$	[21]
	Epothilones B	Tubulin polymerization	—	[33]
	Discodermolide	Tubulin polymerization	—	[34]
Lalmalide/peloruside A site	Laulimalide	Tubulin polymerization	—	[35, 36]
	peloruside A	Tubulin polymerization	—	[35, 36]

made great progress. Some studies have found that some traditional Chinese medicines can inhibit tumors. For this reason, whether the components or analogues of traditional Chinese medicine can be developed as tubulin inhibitors. This provides ideas for the development of high-efficiency and low-toxicity tubulin inhibitors in the future.

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Conflict of Interest

The authors declare no conflict of interest.

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