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Review

Natural antitubulin agents: Importance of 3,4,5-trimethoxyphenyl fragment

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ABSTRACT

Microtubules are polar cytoskeletal filaments assembled from head-to-tail and comprised of lateral associations of α/β-tubulin heterodimers that play key role in various cellular processes. Because of their vital role in mitosis and various other cellular processes, microtubules have been attractive targets for several disease conditions and especially for cancer. Antitubulin is the most successful class of antimitotic agents in cancer chemotherapeutics. The target recognition of antimitotic agents as a ligand is not much explored so far. However, 3,4,5-trimethoxyphenyl fragment has been much highlighted and discussed in such type of interactions. In this review, some of the most important naturally occurring antimitotic agents and their interactions with microtubules are discussed with a special emphasis on the role of 3,4,5-trimethoxyphenyl unit. At last, some emerging naturally occurring antimitotic agents have also been tabulated.

Contents

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1. Introduction

Tubulin is a globular protein produced in all eukaryotic cells.[1] The term 'tubulin' was originally coined by Prof. Hideo Mohri, University of Tokyo, in 1968 as it is a constituent protein unit of microtubule. There are five distinct types of tubulins namely alpha, beta, gamma, delta, and epsilon. Recently, a sixth member zeta tubulin has also been discovered in kinetoplastid protozoa, that is, prokaryotic cells.[2] Tubulins are highly conserved protein class with as many as 7 isotypes of α-tubulin and 8 isotypes of β-tubulin in human. Among these, α and β-tubulins are the most common and mostly exist as heterodimer. Both α and β-tubulin bind spontaneously to form a heterodimer fundamental subunit of about 100 kDa, where α-subunit is −ve end and β-subunit is +ve (fast growing) end.[3] This dimerization process is regulated by feed-back mechanism.

Microtubules are the rigid hollow cylinders built by polymerization of these subunits of tubulin dimers. Here, polymerization is a reversible process where tubulin dimers bind non-covalently to microtubule in forward reaction and microtubule is de-polymerized to tubulin dimers in backward reaction. In this process, first basic linear polymer structure called protofilaments are formed which in turn assemble into microtubules. Both α and β monomer bind to guanosine-5′-triphosphate (GTP), in α-tubulin the GTP remains buried inside while β-tubulin bound GTP remains exposed to outside. The bound GTP of β-tubulin is hydrolysed to guanosine-5′-diphsophate (GDP). GTP hydrolysis is required for microtubule dynamics and caps of GTP bound tubulin stabilizing microtubule plus end has been reported. When these caps are hydrolysed, rapid depolymerisation occurs.[4]

The binding of β-subunit to GTP or GDP influences the stability of the dimer in microtubule. Here GTP stabilizes forward reaction while GDP influences backward reaction. This is also known as microtubule growing and shrinking stages or growth and shortening phases. This process of tubulin dimer adding at + end and falling at − end is also known as 'treadmilling'. Although microtubule formation has an intrinsic instability, the overall process is in dynamic equilibrium. Two contradictory models have been proposed for tubulin-microtubule dynamics. 'The allosteric model' states that after binding with GTP, αβ-tubulin adopts a more polymerization conducive conformation for lateral interactions.[5–7] While, 'The lattice model' states that conformational changes occur only upon recruitment into growing lattice. Thus, conformational changes are consequences of lattice assembly here.[8] A blended model has also been proposed in which free dimer allosteric effects retain importance in an assembly process dominated by lattice induced effects.[9] The rate of stabilization and destabilization is induced by some proteins known as microtubule-associated proteins (MAPs). The modulation of these protein-protein interactions is very much important to induce stabilization or inhibitory effects in drug development.[10]

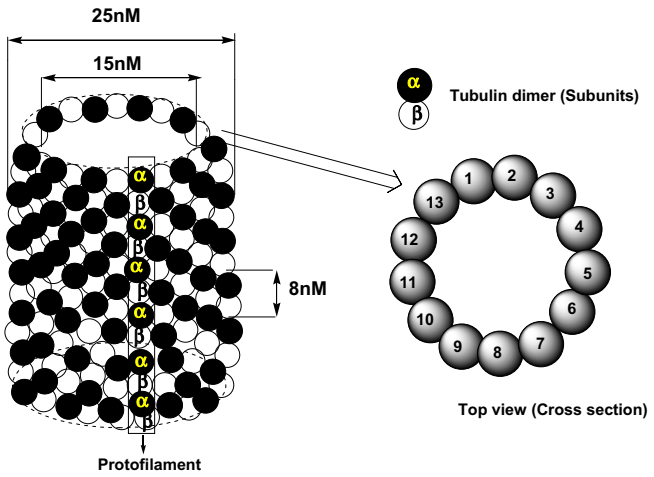

Figure 1. Structures of tubulin dimer and microtubule.

Microtubules are tube-like long hollow cylindrical filamentous structures (Fig. 1). Every microtubule is a simple tube built usually from 13 protofilaments. But, this number can vary in rare cases. With a 24 nM diameter microtubules can be 25–50 μm long. They serve as cytoskeletons of the cells and also form framework for structures like spindle apparatus that helps in chromosome segregation during cell division. Microtubules are also proposed as 'molecular highways' for the transport of cellular material from one part of cell to another with the help of microtubule binding proteins as carriers. Other functions of microtubule include cell motility and cell polarity. Microtubule assembly is vital for many fundamental cellular processes.[11] A subset of microtubules exists as fused structures where tubule A is fused with another tubule (mostly B and occasionally with C) to form ciliary axonemes (microtubule doublets) or centrioles and basal bodies (microtubule triplets). A variety of microtubule based structures are known, but the process of their formation and their functions is still unclear.[12] The dynamic instability of microtubules has a crucial role in mitosis. The microtubule array present in interphase cells disassembles and the free tubulin subunits are reassembled to form mitotic spindle which is responsible for the separation of daughter chromosomes. This restructuring of microtubule cytoskeleton is directed by duplication of the centrosome to form two separate microtubule organizing centres at opposite poles of the mitotic spindle. Microtubule dynamicity increases twenty to hundred fold while the nucleation rate of microtubules at the centrosome is increased by seven fold during mitosis. The process of 'tubulin-GTP assembly' and 'tubulin-GDP disassembly' helps in capturing chromosomes during prometaphase, then for the attachment of spindle fibres to kinetochores known as microtubule springing in metaphase for precise alignment which acts as check-point for metaphase-anaphase and at last movement of chromosomes.[13] Recently, formin proteins have been recognised as prominent regulators of microtubule dynamics. Formins modulate the interphase and mitosis of specific microtubules.[14] However, this area is less explored and needs special emphasis. Thus, microtubule dynamics plays a crucial role in mitotic process which perfectly takes care and dictates the various events to complete the process to get two identical sets before cleavage of the cell into two daughter cells. Overall, microtubules play diverse roles in cellular structure and function. Thus, owing to their crucial role in mitotic process, microtubules have become an attractive target and the drugs that affect microtubule assembly by disturbing the machinery are useful especially in the treatment of cancer. In addition to cancer, several other diseases also have correlation with malfunctioning of microtubule assembly. Several neurodegenerative diseases like