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REVIEW ARTICLE

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Microtubular Organization and Dynamics: Synthetic Chemistry, Chemical Biology, Biotechnology, Medicine and Biomedicine Perspectives

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Abstract

Microtubules are important cytoskeletal structures that provide mechanical support, motility, intracellular transport, chromosome segregation, and cytoplasmic organization. They participate in several cellular processes related to intracellular transport, including the movement of organelles, mRNA, secretory vesicles, and macromolecular assemblies within the cell. The structure and organization of microtubules have been elaborated in the present article with illustrations of tubulin heterodimers, protofilaments forming a single linear chain, a longitudinal side view showing a stable structural lattice, seam, and the cross-sectional view of parallel protofilaments. The structure and organization of microtubules have been described using information on structural polarity, nucleation, polymerization, and dynamics. Furthermore, some basic concepts regarding the interaction between microtubules and ion channels and biochemicals have also been included. Some of the unsolved issues about the basic concepts have been pointed out. The present review, in general, provides information on microtubular organization and dynamics from the perspectives of synthetic chemistry, chemical biology, synthetic biology, biotechnology, and medicine/biomedicine. Future studies will clarify the unresolved issues related to microtubular structure, organization, dynamics, and interactions with ion channels and biochemical/physiological/pathophysiological factors. **(International Journal of Biomedicine. 2026;16(4):455-461.)**

Keywords: microtubular structure • organization and dynamics • nucleation • polymerization • ion-channels • biochemicals

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Abbreviations

CS, chitosan; **GDP,** guanosine diphosphate; **GTP,** guanosine triphosphate; **γ-TuRC,** γ-tubulin ring complex; **Hcy,** homocysteine; **ILs,** interleukins; **ITZ,** itraconazole; **MTOC,** m**icrotubule organizing center; PLEKHA7,** pleckstrin homology domain-containing family-A member-7; **ST-CS,** N-stearoyl chitosan; **TRP channels,** transient receptor potential channels; **TRPM8:** transient receptor potential melastatin-8; **VitD,** vitamin D.

Introduction

The cytoskeleton is a structural network in the cell's cytoplasm, and microtubules are part of it. Microtubules are important cytoskeletal structures that provide mechanical support, motility, intracellular transport, chromosome segregation, and cytoplasmic organization.[1] These structures are present in cilia and flagella.[2] Microtubules are rigid filaments, but hollow tube-like cylinders made up of biopolymers of globular tubulin proteins. They form the internal structural framework of eukaryotic cells. They serve as microscopic roadways for intracellular transport and are involved in structural support, maintaining the shape of the cell, and separating the chromosomes into two daughter cells during cell division by forming the mitotic spindle.[3] They are considered the tracks for the walk of motor proteins kinesin and dynein for the transport of materials, including the movement of the organelles and vesicles in the cell. Growth and shrinkage of microtubules generate force.

Microtubules bind to many proteins, including the motor proteins (dynein and kinesin), the microtubule-binding protein katanin, and a variety of proteins involved in regulating microtubular dynamics.[4] They take part in several cellular processes related to intracellular transport,

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including the movement of organelles, mRNA, secretory vesicles, and macromolecular assemblies in the cell.[3,5,6] Their mechanics influence cellular and molecular processes, as well as cell morphology.[7] The cell locomotion associated with microtubule-like processes observed quite early was confirmed later with biochemical techniques and electron microscopy.[8] Microtubules are termed neurotubules during the development of neurons, and they can control the dynamics of actin, which is another cytoskeletal component.[9]

The cell types have variations in microtubular organization. Sites of cell-cell contacts and their organization along the apical-basal axis for microtubular minus ends in epithelia, and, after nucleation, the release of minus-end re-anchoring in peripheral areas by ninein, PLEKHA7 (Pleckstrin homology domain-containing family-A member-7), etc.,[10] help transport vesicles, organelles, proteins, etc., along the apical-basal axis. Microtubules in fibroblasts and mesenchymal cells anchor at the centrosome and spread with plus ends towards the periphery of the cell, helping in cell migration.

There is a significant role for membrane potentials,[11-18] membrane interactions,[19,20] ion channels,[21-25] and a variety of physiological/biochemical factors in various diseases/disease conditions.[26-33] Interaction of the ion channels occurs with the microtubules for transport and other functions. At the same time, the physiological/pathophysiological variables influence the structure, organization, dynamics, and activity of microtubules. The present review provides important information on microtubular organization and dynamics, employing concepts and modern techniques and methods from synthetic chemistry, chemical biology, synthetic biology, biotechnology, medicine, and biomedicine.

Structure and Organization of Microtubules

Microtubules are long, rigid, and hollow cylinders composed of α- and β-tubulin dimers. The microtubules have a lumen or inner hollow space. Almost 50% of the amino acids are identical in the α and β types of tubulins. The molecular weight of each of them is about 50 kDa. The fundamental microtubular subunit is a dimer composed of two globular proteins (alpha-tubulin and beta-tubulin) that are tightly bound to each other (Fig. 1). In other words, tubulin heterodimers are fundamental building blocks of microtubules, composed of alpha- and beta-tubulin polypeptides linked noncovalently.[34-36]

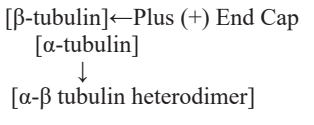


Fig. 1. *Tubulin heterodimers.*

Each heterodimer weighs 55 kDa and consists of closely related globular alpha and beta monomers. They have asymmetric nucleotide-binding protein surface pockets: alpha tubulin on the N-site (tightly and non-exchangeably/non-hydrolyzably binds GTP (guanosine triphosphate)), and beta tubulin on the E-site (reversibly binds GTP for hydrolyzing it to GDP exchangeably).[36]

The protofilament is a linear chain of repeating tubulin heterodimers end-to-end, forming a long string; the linear protofilaments are formed by polymerization of α/β-tubulin dimers, forming a single microtubule. The addition of further α/β-tubulin dimers may then extend this microtubule. Their stacking is always in the same direction: alpha matches up with beta, and the directional orientation or polarity is established by the filament (Fig. 2). When viewed from the side, a stable structural lattice is observed, formed by the hollow interior and the repeating dimers (Fig. 3).

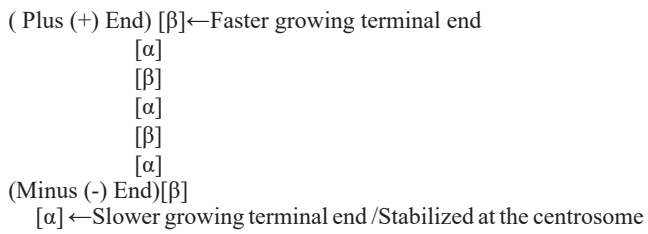


Fig. 2. *Protofilaments forming single linear chain.*

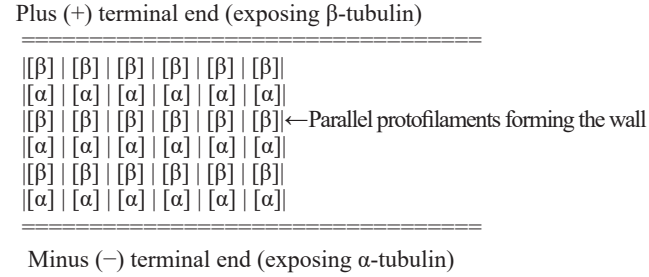


Fig. 3. *Longitudinal side view showing a stable structural lattice*

The microtubule, forming a hollow cylinder of protofilaments in cross section, is seen as a ring structure of 13 protofilaments (1-13 linear protofilaments forming the tube wall), containing alpha- and beta-tubulins alternatively in a circular geometry. Instead of the perfect alternation, the alpha subunits touch the alpha subunits laterally between the 7th and 8th protofilaments, creating a seam (Fig. 4).

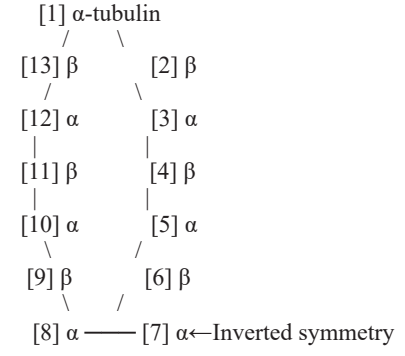


Fig. 4. *Seam-a ring containing a standard 13-protofilament microtubule.*

To form the hollow wall of a microtubule, 13 protofilaments, aligned in parallel, typically align side by side, representing alternative alpha and beta subunits (Fig. 5).

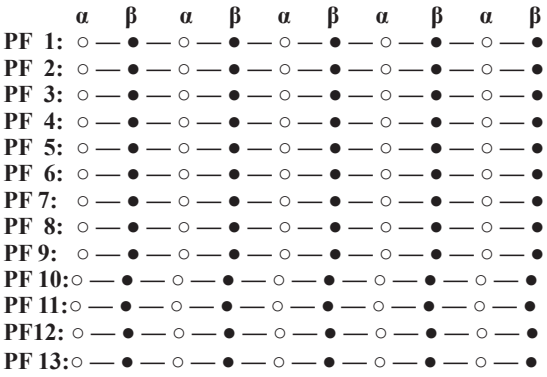


Fig. 5. *Cross-sectional view of parallel protofilaments.*

Each protofilament is made of a string of α-tubulin and β-tubulin. Thirteen parallel protofilaments, aligned side by side, wrap around each other and form a hollow, straw-like tube or standard microtubule, though fewer or more protofilaments in microtubules have been observed.[37]

The elongation at the plus (+) end (with exposed β-subunits of a tubulin dimer) is rapid compared with that at the minus (-) end (with exposed α-subunits of a tubulin dimer). In other words, α-subunits are exposed in one end, whereas β-subunits are exposed in the other end in a protofilament. Furthermore, protofilaments bundle in parallel with the same polarity.[38]

Side-by-side or lateral association or bonding of protofilaments forms a sheet that rolls up to assemble a cylindrical microtubule wall.[37] Resultantly, the association between adjacent protofilaments provides the required structural rigidity and strength to the microtubules.

Table 1.

Structure and organization of microtubules.

Structures/ structural features	Specific characteristics/structural organization
Subunits	Alpha and beta tubulins; they bind together non-covalently and form the building block of microtubules
Protofilaments	Head-to-tail assembly of the tubulin dimers forming thirteen linear/ parallel protofilaments that associate linearly and make a hollow wall of the tube of each microtubule
Associated regulatory motors	Kinesins and dyneins are associated regulatory motor proteins that move along microtubules using ATP hydrolysis to transport vesicles and organelles. Kinesins (anterograde motors) move to the plus (+) terminal end, and the dyneins (retrograde) move to the minus (-) terminal end
Structural polarity	Fast growing/dynamic plus (+) end is terminated by beta-tubulin, whereas the anchored, stabilized, and slow-growing minus (-) end is terminated by alpha-tubulin
Tube dimension	Length may vary from a few hundred nanometers to several micrometers, whereas the inner lumen diameter is around 15 nanometers and the outer diameter is about 25 nanometers
Dynamics of assembly (instability)	Rapid growth or polymerization and sudden shrinkage or depolymerization, in a continuous cycle, are driven by GTP (guanosine triphosphate) binding and hydrolysis on beta-tubulin, manifesting dynamic instability. Catastrophe is the rapid disassembly.
Nucleation and anchoring	The minus (-) ends are anchored, e.g., at the centrosome (microtubule organizing center) by gamma-tubulin ring complexes, which serve as templates for assembly.

Table 2.

Structural polarity.

Structure/related features	Minus (-) terminal end	Positive (+) terminal end
Terminal subunits	Alpha-tubulin exposed	Beta-tubulin exposed
Anchor	At MTOC in centrosome	Cell periphery/ outward
Growth rate	Stable, slow growing	Rapidly grows and shrinks/dynamic
GTP cap	Locked/protected from disassembly	Active growth present stabilizing GTP cap
Instability	Low level of activity as it is stable/dormant	Constant transitions showing high activity in sudden catastrophe & rescue periods
Motor proteins	Dyneins (retrograde)	Kinesins (anterograde)
Nucleation	Capped/stabilized by gamma-tubulin ring complexes	Freely performs rapid elongation

The Pseudo-helical structure forms via lateral bonding of protofilaments, in which one turn of the helix contains 13 tubulin dimers from different protofilaments.[39] However, the microfilaments can have other forms, e.g., helical filaments in protists.[40]

Two types of lattices can appear in the subunits of the lateral protofilaments in a microtubule. These are A-type and B-type. If protofilaments bond between adjacent α and β-subunits of tubulin, this constitutes an A-type lattice. If the α and β subunits from one protofilament associate with the α and β subunits from another adjacent protofilament, it is a type-2 lattice, the primary microtubular arrangement.[41] Nucleation and Polymerization

The critical, rate-limiting first step in the formation of microtubules, when α- and β-tubulin dimers aggregate into a nucleus or initial seed that supports rapid filament polymerization, is called microtubule nucleation.[42] Microtubule nucleation starts the formation of microtubules under the well-organized system- microtubule organizing centers (MTOCs) that contain another tubulin-γ-tubulin (different from α- and β-tubulin subunits), which forms a structure called the γ-tubulin ring complex (γ-TuRC) for starting the polymerization by acting as a template for α/β-tubulin dimers and serving as a cap at the minus end where the growth of microtubules continues on the plus side and away from the MTOC.

The Golgi bodies can also act as a nucleation platform for microtubules.[43] However, centrosomes are considered the primary MIOC in most cells; e.g., MTOCs for cilia and flagella are located at their bases, called basal bodies. Centrosome nucleation is symmetrical inherently. However, the Golgi-related nucleation presents asymmetry. Furthermore, augmin, a protein complex, is an important factor in centrosome-associated microtubule formation and binds γ-TuRC to increase microtubule density around the mitotic spindle origin.[44] Interaction of α- and β-tubulin dimers occurs during the microtubular nucleation process, forming a stable seed (the start of microtubule polymerization via elongation, enabling the rapid attachment of additional dimers to form the hollow, cylindrical microtubules).

Dynamics of Microtubules

To exhibit the dynamics, the ends of a microtubule rapidly switch back and forth dynamically between growing (assembly) and shrinking (disassembly).[45] Tubulin dimers bind two GTP molecules (non-exchangeable alpha-tubulin site and exchangeable beta -tubulin site). Still, the GDP on the beta-tubulin subunit is hydrolyzed after the dimer joins the growing microtubule.

During polymerization, tubulin dimers are GTP (guanosine-5'-triphosphate)-bound to the beta-tubulin subunit, enabling the stable addition and growth of microtubular structures with dynamic instability.[46] The GTP bound to α-tubulin serves as a non-exchangeable, permanent, and non-hydrolyzable structure, and is stable, playing a structural role (maintaining the proper shape/integrity of the tubulin heterodimer) in this bound state. The assembly properties of GDP-tubulin differ from those of GTP-tubulin: GDP-tubulin falls apart, shrinking the cell's internal skeleton; in other words, it is more prone to depolymerization. In contrast, GTP-tubulin is involved in its assembly and growth.[47]

A catastrophe, or the switch from growth to shrinkage, is a sudden moment when a growing skeletal tube or microtubule stops elongating and begins to fall apart. Whereas the rescue is a process when GTP-bound tubulin begins adding again to the tip of the microtubule and a sudden transition of the microtubule occurs from shrinking to a growing state again.[48] Interactions of Microtubules with Ion Channels and Biochemicals

The microtubules and transient receptor potential (TRP) channels exhibit and maintain a bidirectional physical and functional interaction that controls cellular signaling, channel gating, and cytoskeletal dynamic properties. [21-23,49-53] Microtubules interact with the inner surface of the membrane and help in the regulation of membrane potentials.[25 The interaction among] microtubules, transient receptor potential melastatin-8 (TRPM8) ion channels, and testosterone is involved in regulating sensory transduction, non-genomic hormonal signaling, and cell trafficking.[54-59]

Voltage-gated sodium channels are regulated by microtubules, which serve as intracellular tracks for channel trafficking and anchor them to specific domains of the cell membrane.[60] It was found that the tracking proteins of the plus end of microtubules are important modulators for cardiac sodium channels/ arrhythmogenesis.[60] Regarding the association of voltage-gated sodium channels with microtubules, the electrostatic forces and hydrogen bonding were found to be significantly involved in several medical disorders.[61-63]

Various biochemical factors in medical disorders are associated with structural changes, organization, and dynamics. Some of those are, insulin in diabetes (Shiels et al., 2007),[26] adipokines in diabetes (Kim et al., 2023),[30] interleukins (ILs),[64,65] homocysteine (Hcy),[66-67] vitamin D (VitD),[68,69] cholesterol,[70] adipokines in various medical disorders,[71,72] hepcidin and iron,[73,74] and steroid hormones.[75]

Itraconazole (ITZ) therapy significantly reduces microtubule formation in endothelial cells, which contributes to its efficacy in anti-cancer and anti-angiogenic activities.[76-78] The intersection of itraconazole with N-stearoyl chitosan (ST-CS) was revealed, with the purpose of using chitosan (CS) polymers pharmaceutically as a coating for liposomes for drug delivery of the anti-microtubule agent ITZ for cellular delivery and oncological purposes.[78]

Conclusion

Despite the well-established fundamental concepts regarding the importance of alpha and beta tubulins and how GTP controls dynamic instability, it is still not known how these microtubular subunits regulate complex cellular processes. Furthermore, the structural modifications and alterations at the atomic level occurring in response to physical forces that change the activity of GTPase or the conformation of the lattice are not yet resolved.

In connection with the structural seam, it is not yet clear how the structural discontinuity of the seam occurs and how it is involved in the binding and signaling of certain proteins. As concerns tissue development, the non-centrosomal regulation, along with the exact mechanism by which centrosomes are downregulated, is also not clearly known. Which rules govern the tubulin code have not yet been explored. In vitro 2D cell culture studies of microtubular functions have been conducted. Still, the alterations in microtubular dynamics that occur in 3D tissues in real time, and in 'in vivo' processes/differentiation are largely unexplored. The self-organizational/self-assembly principles governing microtubular linkages under changing stress conditions are not well understood.

A crucial question remains to be solved: how the mechanical load in growing or shrinking microtubules directly influences the conformation of ion channels. Furthermore, there are several other issues in the interaction between microtubules and ion channels. Another complexity is accurately simulating dynamic transitions in multi-subunit ion channels while they interact with the array of non-centrosome microtubules.

The present review provides information on microtubular organization and dynamics from the perspectives of synthetic chemistry, chemical biology, synthetic biology, biotechnology, and medicine/biomedicine. Hopefully, future studies will clarify the unresolved issues related to microtubular structure, organization, dynamics, and dynamic interactions with ion channels, as well as biochemical/physiological-pathophysiological variations.

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This research received no external funding.

Conflicts of Interest

The author declares no conflicts of interest.

Author Contribution Statement

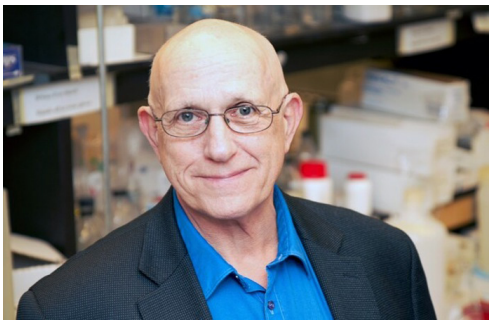
The author confirms responsibility for the conceptualization, design, review, editing, and final writing of the present manuscript.

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Dedication

The author dedicates this article to the loving memory of his mentor and first postdoctoral advisor, Dr. W. McIntyre (Mac) Burnham, Professor Emeritus in the Department of Pharmacology and Toxicology, Temerty Faculty of Medicine, University of Toronto. The author had the privilege of conducting research and collaborating on several funded programs in Dr. Burnham's laboratory, beginning with a postdoctoral fellowship from January 10 to December 31, 1995.



Professor Willets McIntyre (Mac) Burnham (Chicago, 1939 – Toronto, 2024), B.A., Ph.D. Renowned neuropharmacologist, electrophysiologist, neuropsychopharmacologist, epileptologist, and Professor Emeritus, Department of Pharmacology & Toxicology, Temerty Faculty of Medicine, University of Toronto

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