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Reply to Comment on "Photo-Controlled Reversible Microtubule Assembly Mediated by Paclitaxel-Modified Cyclodextrin"

*Ying-Ming Zhang, Qilin Yu, and Yu Liu**

cyclodextrin · microtubules · molecular recognition · photo-responsiveness · supramolecular assembly

In a Correspondence on our previous study "Photo-Controlled Reversible Microtubule Assembly Mediated by Paclitaxel-Modified Cyclodextrin" published in this journal in 2018,[1a] Thorn-Seshold comments on our results.[1b] First of all, we would like to appreciate his comments and interest in our work. The aggregation behavior of microtubules (MTs) in our work has been demonstrated from the viewpoint of macrocycle-based host–guest complexation at the supramolecular level and subsequently, the MT stabilizers based on azobenzene-modified paclitaxel (PTX) derivatives as photoswitchable small molecules have been investigated by Thorn-Seshold and co-workers in 2019.[2]

In our case, the microscopy results showed that the MT morphology was dramatically affected by the photoisomeric complexation between cyclodextrin (CD) and arylazopyrazole (AAP). No fibrous assembly as free MT could be observed in the presence of free PTX-CD, PTX-AAP, or their inclusion complex in the *cis*/*trans* states. Therefore, the introduction of CD and AAP definitely influenced the self-assembling behavior between PTX and MT. Moreover, fluorescent-dye-staining assays demonstrated that the PTX-derived host and guest compounds still possessed MT-targeting ability to some extent, because MT could be co-labeled by FITC-tagged antibodies and adamantane-containing RhB. Thus, the microtubular aggregation was proposed as one of the possible assembling modes in Scheme 1 (cartoon presentation). The binding mode of MT with CD and AAP was directly deduced from our microscopy images and cellular confocal experiments. The biological effect in our work may be jointly attributed to both the PTX-dependent pathway (PTX-induced microtubular stabilization) and the PTX-independent pathway (complexation-induced multivalent supramolecular cross-linkage) at the nanometer scale.[3] Under these circumstances, one reasonable explanation is that the latter (independent) effect may become comparable to the former (dependent) one when the MT affinity is reduced by chemical modification at the 2′-OH position of PTX.

Moreover, as a widely studied macrocyclic receptor in supramolecular chemistry, CD can form a diversity of supramolecular assemblies.[4] To determine the precise binding mode, in addition to the viewpoint of structural biology for evaluating the original PTX–MT interaction at the single-molecule level, many other factors and multiple supramolecular noncovalent interactions (e.g., self-inclusion, self-exclusion, amphiphilicity, extensive hydrogen bonding, and supramolecular multivalency/cooperativity) between PTX-CD and PTX-AAP should also be taken into account. For example, the multivalent inclusion complexation between multiple CD and PTX molecules may confer high stability to the nanoassembly.[5] Therefore, in our opinion, no binding mode can be exclusively confirmed at the present time until the hyperfine structures of such multicomponent CD–protein assemblies have been obtained both in solution and in the solid state (e.g., in a single crystal).

Moreover, azobenzene/CD is one of the most frequently used host–guest pairs in adjusting the assembling/disassembling behavior of proteins and other biomacromolecules.[6] Meanwhile, AAP is a new type of azo compound, which possesses quite distinct photophysical behavior compared to conventional azobenzenes, such as enhanced photostability and photoconversion efficiency. The biological effect of pristine AAP on pure MT may deserve further attention, but this aspect was outside the scope of our previous study.

Overall, based on NMR, TEM, UV/Vis transmittance, and confocal microscopy experiments, we clearly demonstrated in our previous study that 1) the MT self-assembling morphology can be strongly affected by the host–guest complexation between CD and AAP, and that 2) complexation-induced MT aggregation can be realized in a cellular environment. Thus, our work provides an alternative supramolecular chemistry method to modulate a biomacromolecular assembling process. Finally, we would like to thank Dr. Thorn-Seshold for his constructive suggestions and express our hope that we can improve the chemical simulation and

[*] Dr. Y.-M. Zhang, Dr. Q. Yu, Prof. Dr. Y. Liu
College of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University
Tianjin 300071 (China)
E-mail: yuliu@nankai.edu.cn

The ORCID identification number(s) for the author(s) of this article can be found under:
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gain further insight into the biological mechanism in further work.

Conflict of interest

The authors declare no conflict of interest.

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