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The recycling of tubulin heterodimer by tubulin cofactors TBCA, TBCB, and TBCE is blocked by colchicine

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Colchicine has been used to treat gout and effectively prevent autoinflammatory diseases and both primary and recurrent pericarditis episodes. The anti-inflammatory action of colchicine seems to result from a compromised microtubule (MT) networks that affects several inflammatory pathways in cells that mediate immune response like the entire NLRP3 inflammasome. Emerging results show that the MT network is a potential regulator of cardiac mechanics. We have investigated how colchicine impacts tubulin folding cofactors TBCA, TBCB, and TBCE activities required for tubulin heterodimer assembly, recycling cycle, and quality control. We show that the exposure of human cells to colchicine causes the decrease of TBCA/b-tubulin complex and the detection of free TBCA in HeLa cells. Free TBCA was never observed in human control cells nor cells exposed to other MT depolymerizing agents, or even as a result of protein translation inhibition by cycloheximide. The appearance of free TBCA is accompanied by increased free soluble tubulin heterodimers due to MT depolymerization. In *in vitro* assays, we show that TBCB/TBCE cannot dissociate tubulin heterodimers bound to colchicine which affects the heterodimer recycling/quality control. Alteration of TBCA levels, either by RNAi or by overexpression, causes the decrease of tubulin heterodimers. These data strongly suggest that TBCA's primary role is in b-tubulin recycling by receiving b-tubulin from the dissociation of preexisting heterodimers instead of newly synthesized tubulins. Our results point to the hypothesis that, *in vivo*, TBCA concentration determines tubulin fate being it recycling or degradation.The TBCE/TBCB/TBCA triad is also crucial for controlling the critical concentration of free tubulin heterodimers and MT dynamics by recycling the tubulin heterodimers. The finding that TBCA is abundant in insoluble protein extracts of the mice heart and colchicine affects the tubulin heterodimer recycling/degradation system, the TBCE/TBCB+TBCA should be considered in the context of colchicine's therapeutic benefits as an anti-inflammatory drug.
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