Here the molecular mechanism of antimitotic drugs, biological compounds that bind to tubulin and microtubules and suppress microtubule dynamics are reviewed. A common feature of tubulin-interacting compounds is that binding to tubulin is linked to assembly, either the stabilization of a microtubule lattice by compounds like the taxanes and epothilones, or the induction of alternate, nonmicrotubule polymer forms. The nonmicrotubule polymers arise from tubulin heterodimers or at microtubule ends with compounds like colchicine, vinca alkaloids, dolastatin, and cryptophycin-52. Their mechanism of action is strongly coupled to the mechanism of microtubule assembly, especially structural features that affect nucleotide binding, GTP hydrolysis, stabilization of longitudinal and lateral protofilament contacts, and endwise growth and disassembly dynamics. Quantitative analysis of drug binding and microtubule or nonmicrotubule polymer formation can be a useful tool in drug design, as in many cases the energetics are predictive of IC50 values and clinical doses. Furthermore, these drugs allosterically disrupt the regulation of microtubule dynamics, whereas the regulatory factors themselves may play an important role in drug resistance. Thus, the development of compounds that selectively target regulation of mitotic spindle dynamics and kinetochore capture, by chemical genetics for example, may result in useful and effective therapeutic tools.

Key Words: Allosteric regulation; antimitotics; kinetics; microtubules; polymers; thermodynamics; tubulin.
1. INTRODUCTION

To understand how antimitotic drugs work one must understand the mechanism of microtubule assembly and regulation. This can be highlighted by the observation made by Cabral, Raff, and coworkers (1–6) that cells can develop resistance to drugs simply by varying the fraction of tubulin in the microtubule polymers (Fig. 1). Lower the microtubule polymer concentration and the cells become resistant to drugs like taxol (Fig. 1A); raise the microtubule polymer concentration and cells become resistant to drugs like vinblastine (Fig. 1B). Knowing that taxol binds preferentially to microtubules and not tubulin heterodimers, and that vinblastine destabilizes microtubules and favors the formation of vinblastine-induced spirals. Microtubule destabilization can reflect alterations in isotype levels, an increase in activity or concentration of microtubule stabilizers, or a decrease in activity or concentration of microtubule destabilizers (7). (Panel C) This mass action model can easily be extended to include the formation of + end microtubule structures during kinetochore attachment. This can represent a growing (blunt end) or a shrinking (curved end) dynamic conformation; or it could represent conformations that favor or disfavor kinetochore interaction and attachment; or it could represent a microtubule stabilized by Clip-170 or destabilized by MCAK (see Fig. 4 in Chapter 8).

Fig. 1. Alterations in microtubule polymer levels can cause drug resistance. (Panel A) Taxol resistance occurs when microtubules are destabilized (indicated by the large dissociation arrow) thus opposing the formation of taxol-stabilized microtubules. Microtubule destabilization can reflect alterations in isotype levels, a decrease in activity or concentration of microtubule stabilizers, or an increase in activity or concentration of microtubule destabilizers (7). (Panel B) Vinblastine resistance occurs when microtubules are stabilized (indicated by the large association arrow) thus opposing the formation of vinblastine-induced spirals. Microtubule stabilization can reflect alterations in isotype levels, an increase in activity or concentration of microtubule stabilizers, or a decrease in activity or concentration of microtubule destabilizers (7). (Panel C) This mass action model can easily be extended to include the formation of + end microtubule structures during kinetochore attachment. This can represent a growing (blunt end) or a shrinking (curved end) dynamic conformation; or it could represent conformations that favor or disfavor kinetochore interaction and attachment; or it could represent a microtubule stabilized by Clip-170 or destabilized by MCAK (see Fig. 4 in Chapter 8).