Commentary

Amphotericin B still in the headlines

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Invited Commentary on key findings in the literature

Antifungal drugs currently used for the treatment of *Candida* infections include polyenes, azoles, echinocandins, allyamines, and flucytosine. These drugs exert either fungicidal or fungistatic activities by interfering with essential processes.[1] Intensive prophylactic and therapeutic uses of antifungal agents have selected for drug-resistant strains.[2] Moreover, the limited arsenal of antifungal drugs is further compromised by severe side effects in patients and the emergence of species refractory to conventionally used agents. There is a need to develop new antifungals and to explore novel therapeutic approaches to treat *Candida* infections. To widen the repertoire of antifungal drugs, targets that differ from those of conventional drugs have to be identified.

For over forty years, the polyene antibiotic amphotericin B (AmB) has been one of the most important agents used to combat systemic fungal infections.[1] In spite of side effects such as nephrotoxicity, anemia, and cardiac arrhythmia, AmB remains the drug of choice for treatment of immunosuppressed patients, such as cancer patients in intensive chemotherapy, solid organ transplant recipients, and AIDS patients. The interaction of amphotericin B with ergosterol, the fungal-specific sterol, and other membrane sterols, results in the production of aqueous pores. As sterols are responsible for the membrane fluidity, sensitive target organisms lose their cellular integrity. The exact molecular architecture of the AmB channel is under debate; different models for the formation and structure of the AmB channel have been proposed.[3] The sterol-dependent membrane activity of AmB suggests that the observed therapeutic efficacy of AmB might be related to a differential preference between sterols found in cell membranes. In mammalian cells, cholesterol is the major membrane sterol, whereas in fungi it is ergosterol. It has long been known that lipid bilayers containing sterols are uniquely vulnerable to permeabilization by AmB, but it is still not clear whether the therapeutic effect of AmB is caused by the preferential formation and stability of a complex of polyene and ergosterol over cholesterol, or whether the observed effects result from direct sterol binding. Efforts to improve the therapeutic index of this drug would benefit substantially from a more complete molecular understanding of its mode of action.

Enabled by the iterative cross-coupling-based synthesis of a functional group deficient derivative of AmB, Gray *et al.*[4] have discovered that channel formation is not required for potent fungicidal activity of AmB but that AmB primarily kills yeast by simply binding ergosterol. Membrane permeabilization via channel formation represents a second complementary mechanism that further increases drug potency and the rate of yeast killing. This finding clearly indicates that the capacity for AmB to form protein-like ion channels might be separable from its cytocidal effects, sharing this activity with another antifungal polyene macrolide natural product, natamycin, recently found to directly bind ergosterol but not to cause membrane permeabilization.[5] The discovery that sterol binding is actually paramount to the antifungal action of AmB has both conceptual and practically important implications. From a conceptual point of view, the findings lend support to the view that antimicrobial mechanisms that can evade resistance not only exist but are ancient, and the mode of action(s) of AmB and perhaps other molecules is one of them. Moreover, although best studied in mammalian cells, lipid signalling is also now appreciated in microbial cells, particularly in yeasts and moulds. The study of Gray *et al.* accelerates advances in lipid biology and points to lipids as promising new targets in the search for superior antimicrobials that may be less vulnerable to resistance.

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This study is an illuminating example of how strategies of antifungal drug discovery and therapeutic index implementation benefit substantially from a more complete molecular understanding of the mode of action of old and novel drugs.

References

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