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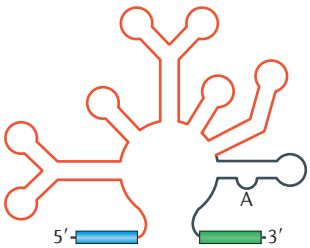
ANTIFUNGAL DRUGS

Small molecules targeting a tertiary RNA structure fight fungi

> Intronistat A and intronistat B inhibited the growth of *C. parapsilosis*

Most currently available small molecules bind to and alter the activity of proteins, but a new study by Fedorova et al. demonstrates that tertiary RNA structures could also be therapeutic targets. They identify compounds that bind to group II introns, RNA structures found in genes that are essential for mitochondrial respiration in plants and fungi, but are not present in vertebrates. These compounds potently inhibit the growth of the pathogen *Candida parapsilosis*, and could therefore be developed as a novel class of therapeutic antifungals.

Group II introns form tertiary structures that act as self-splicing ribozymes; correct intron splicing is needed for translation of these mRNAs. Respiration is important for pathogenic yeast to form biofilms, which colonize medical implant surfaces and are resistant to existing antifungals.



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The authors developed a fluorescent assay to measure the ribozyme activity of a group II intron from *Saccharomyces cerevisiae*. Using this assay, a 10,000-compound library was screened and 16 reproducible hits were identified. Many of these molecules shared common structural elements, which formed the foundation for structure–activity relationship determinants and subsequent compound derivatization to optimize potency. The most potent resulting molecules were named intronistat A and intronistat B. In competition assays, these molecules were highly selective for group II introns.

S. cerevisiae can ferment glucose for energy, but growth on non-fermentable carbon sources such as glycerol requires mitochondrial respiration. Mitochondrial respiration uses cytochrome *c* oxidase subunit 1 (COX1), and *COX1* in *S. cerevisiae* contains a group II intron. Treatment of *S. cerevisiae* with intronistat A substantially reduced the growth in glycerol-containing media. This growth defect could be largely rescued by reintroduction of an intronless version of *COX1*, suggesting that the observed growth defects in intronistat A-treated cells were caused by reduced mRNA splicing and therefore reduced expression of the COX1 protein.

The authors then examined a therapeutically relevant organism, *C. parapsilosis*, which is an important cause of sepsis. Unlike *S. cerevisiae*, pathogens such as *Candida spp.* respire in glucose as well as glycerol, so inhibition of group II introns in these organisms is clinically relevant. *C. parapsilosis* contains a single group II intron in *COX1*. Intronistat A and intronistat B inhibited the growth of *C. parapsilosis* in glucose-containing media with a minimum inhibitory concentration (MIC) of 2–4 μg per ml; a value similar to the MIC for amphotericin B, an antifungal that is currently used for *C. parapsilosis* infection but has substantial toxicity in patients.

This article demonstrates that not only can small molecules bind to tertiary RNA structures to inhibit their processing, but also that such molecules can be found with existing, well-established methods.

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ORIGINAL ARTICLE Fedorova, O. et al. Small molecules that target group II introns are potent antifungal agents. *Nat. Chem. Biol.* https://doi.org/10.1038/s41589-018-0142-0 (2018)
FURTHER READING Warner, K. D. et al. Principles for targeting RNA with drug-like small molecules. *Nat. Rev. Drug Discov.* **17**, 547–558 (2018)