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Harnessing the power of fungal siderophores for the imaging and treatment of human diseases.

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Streszczenie

Innovative strategies are needed to address the current lack of clinically available antifungal drugs and for diagnostic techniques. ‘Repurposing’ of antifungal drugs, similar to techniques currently being utilized with ‘older’ antibacterial drugs in order to combat widespread resistance in the face of a dearth of new drugs, could prove beneficial. Although as yet very limited for fungi, a siderophore-based ‘Trojan Horse’ strategy, in the form of siderophore–antibiotic conjugates, siderophore–fluorescent probe conjugates, or Ga(III)–siderophore complexes, reveals potential clinical relevance and provides a strategy for targeting fungal infections through drug delivery, imaging, and in diagnostics. The application of siderophores against pathogenic fungi is evolving but is still far from its full potential, and further studies are needed to demonstrate their advantages and limitations. One of the biggest obstacles in developing fungus-specific diagnostics and side-effects-free therapeutics is that apart from the fungal cell wall, fungi are metabolically similar to mammalian cells; thus, pathogen-specific targets are extremely limited. One of the few fundamental differences between fungal and mammalian cells lies in the iron acquisition system. The most common mechanism is mediated by small organic chelators – siderophores, often essential for fungal virulence and pathogenicity. Fungi synthesize mainly hydroxamate-type siderophores, which are excreted into the environment, and bind ferric ions with high affinity and selectivity. Delivery of iron-loaded siderophores back to the pathogen occurs via specific membrane receptors and transport proteins. Natural siderophores are generally not species-specific; they exhibit broad-spectrum activity and can be recognized by various types of microorganisms. Moreover, they generally miss proper sites for incorporating additional functionalities; e.g. fluorescent probes, surface-adhesive moieties or drug molecules, to be used for imaging and/or as therapeutic conjugates smuggled into microbial species via siderophore recognition and a ‘Trojan Horse’ strategy. Biomimetic analogues can overcome both these limitations and offer novel tools for both diagnostics and therapeutics. Siderophore mimics with a narrow spectrum of activity offer the possibility of developing selective diagnostic tools, while those with broad-spectrum activity may find therapeutic applications as antifungal drug delivery tools.

Słowa kluczowe

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