

Enzymatic targets for antifungal chemotherapy – current status and perspectives

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Clinical needs for novel antifungal agents have emerged with the rising frequency of fatal mycoses in immunocompromised patients and the switch of spectrum of disseminated fungal infections that has accompanied changes in clinical immunosuppressive therapies. Management of fungal infections is markedly limited by problems of drug safety, resistance (including the multidrug resistance) and effectiveness profiles. Current chemotherapy of invasive mycoses uses a very limited number of antifungal drugs, including amphotericin B, fluconazole, voriconazole and caspofungin. None of them is considered the ideal drug and each demonstrates severe drawbacks and limitations. For these reasons, searching for novel antifungals and for new targets for antifungal drug candidates, is one of the especially urgent challenges of modern chemotherapy.

Almost all novel potential targets for antifungals are proteins and majority of them are enzymes catalyzing reactions that are essential for viability of fungal cells and most often are specific for fungi. Examples of the most promising enzymatic targets for antifungals will be presented, with a special attention focused on three categories: enzymes involved in biosynthesis and assembly of the fungal cell wall, enzymes participating in formation of lipid components of the fungal cell membrane and enzymes catalyzing particular steps in biosynthesis of amino acids. The first category includes glucan synthase, chitin synthase, glucosamine-6-phosphate synthase, and mannosyltransferases, the second one comprises enzymes of ergosterol biosynthetic pathway, inositol phosphorylceramide synthase, serine palmitoyltransferase and *N*-myristoyl transferase and the third one covers homoserine dehydrogenase and enzymes of early steps of lysine and methionine biosynthesis. Perspectives for the rational design of inhibitors of these enzymes as potential antifungal drugs will be discussed.