

Sterol Biosynthesis and Azole Tolerance Is Governed by the Opposing Actions of SrbA and the CCAAT Binding Complex.

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Abstract

Azole drugs selectively target fungal sterol biosynthesis and are critical to our antifungal therapeutic arsenal. However, resistance to this class of drugs, particularly in the major human mould pathogen *Aspergillus fumigatus*, is emerging and reaching levels that have prompted some to suggest that there is a realistic probability that they will be lost for clinical use. The dominating class of pan-azole resistant isolates is characterized by the presence of a tandem repeat of at least 34 bases (TR34) within the promoter of *cyp51A*, the gene encoding the azole drug target sterol C14-demethylase. Here we demonstrate that the repeat sequence in TR34 is bound by both the sterol regulatory element binding protein (SREBP) SrbA, and the CCAAT binding complex (CBC). We show that the CBC acts complementary to SrbA as a negative regulator of ergosterol biosynthesis and show that lack of CBC activity results in increased sterol levels via transcriptional derepression of multiple ergosterol biosynthetic genes including those coding for HMG-CoA-

synthase, HMG-CoA-reductase and sterol C14-demethylase. In agreement with these findings, inactivation of the CBC increased tolerance to different classes of drugs targeting ergosterol biosynthesis including the azoles, allylamines (terbinafine) and statins (simvastatin). We reveal that a clinically relevant mutation in HapE (P88L) significantly impairs the binding affinity of the CBC to its target site. We identify that the mechanism underpinning TR34 driven overexpression of cyp51A results from duplication of SrbA but not CBC binding sites and show that deletion of the 34 mer results in lack of cyp51A expression and increased azole susceptibility similar to a cyp51A null mutant. Finally we show that strains lacking a functional CBC are severely attenuated for pathogenicity in a pulmonary and systemic model of aspergillosis.

Beteiligte Forschungseinheiten

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