Unlocking DNA Adenine Methylation–Based Regulation for Novel Mucormycosis Therapies

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Mucormycosis, caused by fungi of the order *Mucorales*, is among the most lethal fungal infections in humans, characterized by extremely high mortality rates and a striking scarcity of effective therapeutic options. Moreover, existing treatments are often associated with severe toxicity, underscoring the urgent need for new and safer therapeutic strategies. We have uncovered a conserved and essential fungal epigenetic regulatory pathway based on symmetric N6-methyladenine (6mA) that plays a central role in controlling growth and virulence in *Mucorales*. Although 6mA is also present in the human genome, it occurs at extremely low levels and predominantly in an asymmetric configuration, in which only one DNA strand is methylated at each site, in contrast to the symmetric modification where both strands carry the mark. This fundamental difference suggests that pharmacological inhibition of symmetric 6mA deposition could selectively target *Mucorales* while minimizing toxicity to human cells. Importantly, we have identified and characterized the methyltransferase complex responsible for establishing this symmetric modification in fungi and confirmed its absence in humans. *In vivo* inhibition of this complex resulted in reduced virulence in mice, along with altered expression of key virulence factors. Together, these findings open the door to the development of first-in-class antifungal epidrugs that target an epigenetic modification rather than cellular components, representing a shift in antifungal drug discovery.