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Novel cell-killing mechanisms of hydroxyurea and the implication towards combination therapy for the treatment of fungal infections

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Mutations in the *hem13-1* (heme synthesis) and *erg11-1* (ergosterol biosynthesis) pathways genes significantly sensitize the fission yeast *Schizosaccharomyces pombe* to the ribonucleotide reductase inhibitor hydroxyurea (HU). Our results have also shown that treatment with small molecule inhibitors of the enzyme Erg11 and heme biosynthesis phenocopies the *erg11-1* and *hem13-1* mutants in sensitizing wild type cells to HU. HU interacts synergistically with several Erg11 inhibitors and the heme biosynthesis inhibitor sampangine in suppressing cell growth or inducing cell death in *S. pombe*. Importantly, the synergistic drug interactions are likely conserved in eukaryotes because similar synergism has been seen observed in phylogenetically divergent yeast *Saccharomyces cerevisiae* and the opportunistic fungal pathogen *Candida albicans*. Based on our genetic data in *S. pombe*, combinations of sampangine with Erg11 inhibitors are found to be remarkably synergistic in inducing the cell death in *C. albicans*. Together, these results strongly suggest that HU, sampangine and the Erg11 inhibitors can be further developed in drug combinations for the treatment of fungal infections or other diseases such as cancer. Our results suggests that the combination therapy has the potential to tackle various issues associated with single drug therapy such as toxicity to the hosts, less therapeutic effect, narrower spectrum of activity and more importantly, the development of drug resistance.

Biography

Amanpreet Singh is a Post-doctoral Fellow at Mycology Lab, Wadsworth Center, New York State Department of Health, USA. He has obtained his PhD from Department of Biochemistry and Molecular Biology from Boonshoft School of Medicine, Wright State University, Dayton, Ohio, USA. His research interests comprise understanding the molecular mechanism of DNA replication checkpoint pathway and fungal pathogenesis.

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