

Species-specific activity of antibacterial drug combinations

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Abstract

Drug combinations and drug repurposing can act as a first line of defense against the alarming rise of multi-drug resistant (MDR) bacterial infections, yet their current use in clinics is limited. To better understand the potential of drug combinations, we profiled nearly 3,000 combinations of different antibiotics, selected human-targeted drugs and food additives in 6 strains from three clinically-relevant Gram-negative pathogens, *Escherichia coli*, *Salmonella Typhimurium* and *Pseudomonas aeruginosa*, at different drug dose. Although the three species are phylogenetically closely related, more than 70% of the detected drug-drug interactions are species-specific and 21% are even strain-specific, highlighting a vast potential for narrow-spectrum and individualized therapies. Overall, antagonism is twice as common as synergy, but synergies are more conserved across species. While antagonism is almost exclusive between drugs targeting different cellular processes, synergy is enriched in drugs targeting the same process, with both having direct mechanistic implications. To probe the potential clinical utility of the discovered drug synergies, we demonstrated that eight of them are effective against clinical multidrug resistant (MDR) *E. coli* or *Klebsiella pneumoniae* isolates, and one could revert colistin resistance.