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Current Opinion in Microbiology

Antimicrobial interactions: mechanisms and implications for drug discovery and resistance evolution

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Combining antibiotics is a promising strategy for increasing treatment efficacy and for controlling resistance evolution. When drugs are combined, their effects on cells may be amplified or weakened, that is the drugs may show synergistic or antagonistic interactions. Recent work revealed the underlying mechanisms of such drug interactions by elucidating the drugs' joint effects on cell physiology. Moreover, new treatment strategies that use drug combinations to exploit evolutionary tradeoffs were shown to affect the rate of resistance evolution in predictable ways. High throughput studies have further identified drug candidates based on their interactions with established antibiotics and general principles that enable the prediction of drug interactions were suggested. Overall, the conceptual and technical foundation for the rational design of potent drug combinations is rapidly developing.

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Current Opinion in Microbiology 2015, **27**:1–9

This review comes from a themed issue on **Microbial systems biology**

Edited by **Eric Brown** and **Nassos Typas**

http://dx.doi.org/10.1016/j.mib.2015.05.008

Introduction

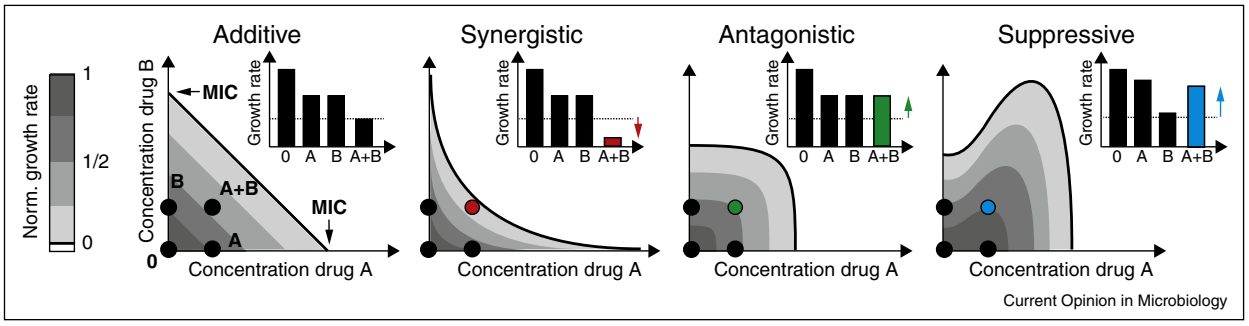
Drug combinations are increasingly used in the treatment of many conditions and diseases including tuberculosis and cancer [1,2]. The interaction between two drugs is synergistic if the joint effect of the drugs is stronger than an additive expectation and is antagonistic if it is weaker [3,4] (Figure 1). Suppression is an extreme kind of antagonism in which one drug alleviates the effect of the other (Figure 1). Synergistic antibiotic pairs such as the well-known combination of trimethoprim with sulfonamides have been applied for decades as they can reduce side-effects and increase the potency of drugs that are ineffective alone [5]. Despite notable exceptions [6], the discovery rate of new antibiotics is in decline while antibiotic resistance in pathogens is rapidly increasing [7–9]. Drug combinations offer potential strategies for controlling the evolution of drug resistance [10–12,13•,14,15••,16••,17,18]. They are further used in basic research as a means of perturbing multiple cell functions to reveal relationships in cell physiology [19,20], analogous to genetic epistasis measurements [21].

Despite their growing biomedical relevance, fundamental questions about drug interactions remain unanswered. In particular, little is known about the underlying mechanisms of most drug interactions. A strategy for designing drug combinations that can slow resistance evolution also remains elusive. Still, our understanding of how antibiotic combinations affect microbes has advanced considerably in recent years. Specifically, networks of pairwise interactions for large numbers of drugs were quantified and in a few cases, the underlying mechanisms of drug interactions were characterized. Furthermore, new drug discovery strategies identified candidates for drugs that synergize with established antibiotics. Several studies provided insights into the effects of drug combinations on resistance evolution. Finally, general principles that hold across drugs and target organisms promise the possibility to predict drug combination effects. This article summarizes new developments in the investigation of antimicrobial drug combinations and focuses on basic research from the last three years; additional aspects and earlier work in the field have been reviewed elsewhere [22,23•,24–27].

Drug interaction networks and the underlying mechanisms of drug interactions

Systematic measurements of drug interaction networks revealed that drug interactions occur frequently and are partly predictable. First, the entire network of pairwise interactions between 20 antibiotics representing the main modes of action was measured in *Escherichia coli* [28]. This drug interaction network is highly structured: the mode of action of the drugs that are combined largely determines the interaction that occurs between them (Figure 2). In principle, this property enables the identification of a new drug's mode of action by simply measuring its interactions with other drugs [28]. Analysis of the interaction network of antifungal drugs in *Saccharomyces cerevisiae* revealed that certain drugs tend to form network hubs, that is they have synergistic or antagonistic interactions with many other drugs [29–31]. Multiplexed screening of ~500 000 drug pairs against HIV identified new synergistic pairs [32]. While such high-throughput techniques are powerful, the systematic investigation of all possible combinations of large numbers

Figure 1

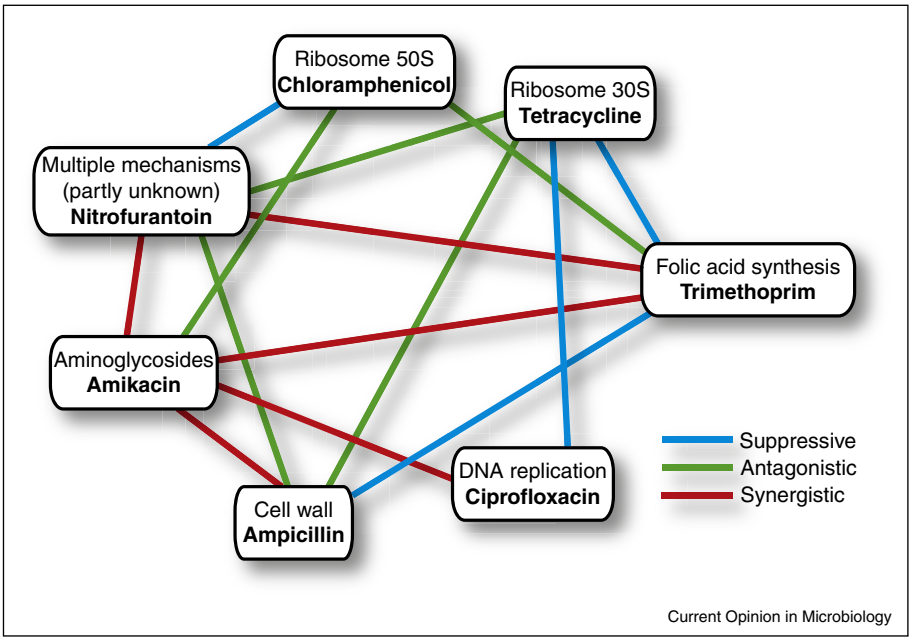


Drug interactions are defined by the shape of lines of equal effect in two-drug concentration space. Schematics showing growth rate (grayscale) and minimal inhibitory concentration (MIC) line (black, line of zero growth) in the two-dimensional concentration space of drugs A and B. The additive reference is given by linear interpolation of the MICs of the individual drugs [3]. For synergistic and antagonistic drug interactions the MIC line lies below or above this additive expectation, respectively. Suppression is a hyper-antagonistic case in which drug A alleviates the effect of drug B. Insets: growth rates in the absence of drugs ('0'), and at fixed concentrations of drugs A and B individually and combined ('A+B'). The dashed horizontal line in insets indicates the additive expectation [4].

of compounds quickly becomes infeasible due to a combinatorial explosion. This limitation becomes even more severe if the drugs are administered in different temporal sequences which can considerably improve clearance compared to simultaneous administration [33]. In the long run, large-scale screens for potent drug combinations must be complemented by approaches that characterize the effects of drug combinations on cells in detail.

One important approach is to characterize the underlying mechanisms of drug interactions which are still largely unknown. The constituent drugs' modes of action and pharmacodynamics alone cannot explain drug interactions in an obvious way [34]. Drug interactions can be caused by relatively simple uptake effects, for example synergism results if one drug increases the permeability of the cell envelope to another drug [35]. Indeed, such an uptake effect likely causes the synergism between aminoglycoside

Figure 2



Example antibiotic interaction network in *E. coli*. The nodes of this network are key antibiotic classes labeled by their main target or mode of action and a representative drug. Edge colors indicate the drug interactions that are typically observed in *E. coli* between the different antibiotic classes: red, synergism; green, antagonism; blue, suppression. No line is shown for additive interactions. Data compiled from [10,28,42] and unpublished results. For clarity, relatively few antibiotics are shown; for a more comprehensive network, see [28].