CLINICAL IMPLICATIONS OF BASIC RESEARCH

Principle of System Balance for Drug Interactions

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Combination drug therapy — the simultaneous administration of more than one medication to treat a single disease — has many diverse applications, including the treatment of microbial and viral infections and cancer. Designing new therapeutic drug combinations, however, can be challenging, because drugs often interact in nontrivial ways. Even a simple pairwise combination of any two drugs can produce diverse outcomes. Synergistic drug combinations, which are more effective than predicted through summing the individual effects of the constituent drugs, are highly sought after, since they often require a reduced dose of the drugs that are administered. But drug combinations may also be antagonistic or even suppressive, leading to cases in which the combined effect is weaker than that of each of the drugs in isolation. A better understanding of how such effects arise would benefit the rational development of combination therapies.

A systematic study of the topic by Bollenbach and colleagues[1] was therefore welcome. The investigators had previously observed an unusual suppressive interaction while quantifying the effects of two-drug combinations on the growth of *Escherichia coli.*[2] The antigrowth effect of antibiotics from a class of DNA-synthesis inhibitors was partially reversed when combined with drugs from a second class, protein-synthesis inhibitors. This observation suggested a mechanistic hypothesis in terms of resource allocation and optimal conditions for growth, which in the most recent study they modeled mathematically and tested with a series of quantitative experiments, using drug perturbations and genetics.

Bollenbach et al. arrived at a charmingly simple explanation for the suppression. When inhibitors of DNA synthesis are administered to bacteria, the optimal balance of protein and DNA levels in the cells is tipped toward a high protein
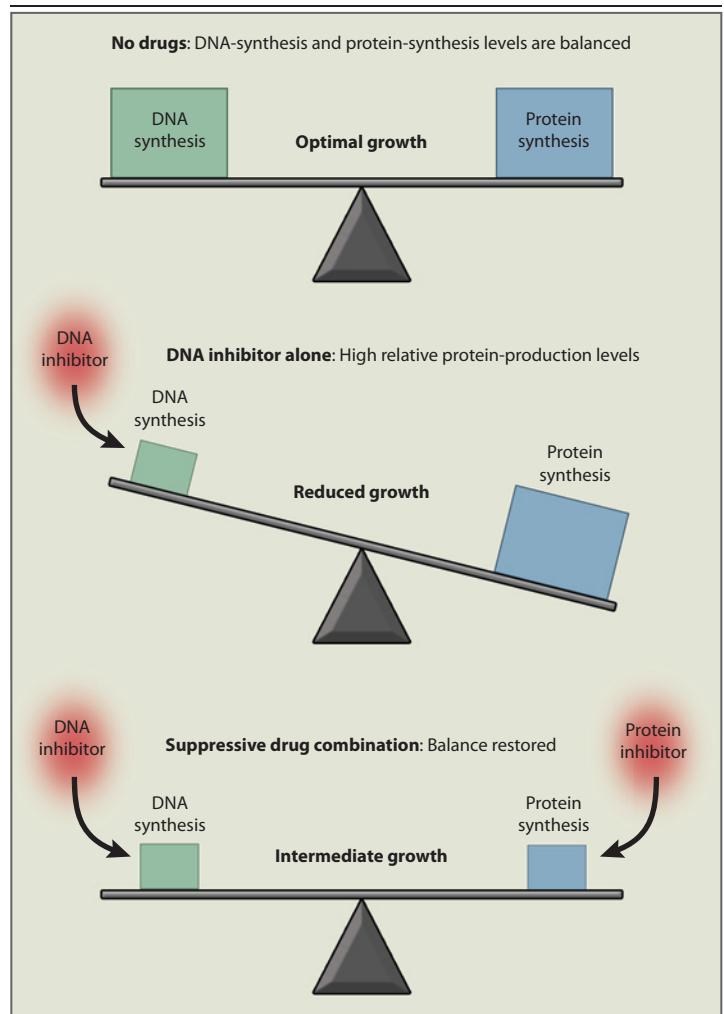

Figure 1. Suppression and Balance in Drug Interactions.

The suppressive effect that antibiotic inhibitors of protein synthesis have on inhibitors of DNA synthesis is shown on the basis of system balance, as discussed by Bollenbach et al.[1] Although an inhibitor of DNA synthesis disrupts the optimal intracellular balance of resource allocation between DNA synthesis and protein production toward excessively high protein levels, the balance can be restored by an inhibitor of protein synthesis, causing drug suppression.

level. Down-regulating ribosomal synthesis in response to DNA stress could correct the imbalance by reducing the rate of protein synthesis. However, as transcription reporter experiments have shown, these cells lack the ability to carry out such regulation. Add a second antibiotic that inhibits protein synthesis, however, and the balance between DNA and protein may be restored, implying more balanced use of metabolic resources and leading cells to recover in growth rate — the opposite of what might be expected (Fig. 1).

An appealing new way of interpreting drug interactions (even beyond microbial systems) is that optimal cell physiological functioning depends on intracellular balances and that drugs disrupt that balance, rather than simply affecting the output of one pathway. In cancer, it is already well known that drugs of different classes that act on different pathways can potentiate each other either additively or synergistically when used in combination.[3] What is usually not known is which cellular balance might be affected by the action of each drug, a potentially interesting area of research.

Cancer biologists may discover situations in which the individual action of two or more drugs disrupts the same physiological balance in the cell in complementary ways, so that their combination restores the balance and at least partially undoes the therapeutic effect of a single drug. Such drug combinations should be avoided. On the positive side, suppressive interactions can be a tool to investigate systematically the mechanisms that regulate key intracellular balances and their effect on the state of cells, such as growth or differentiation. For clinical benefit, one may be able to exploit the principle of balance and rationally design drug combinations that disrupt the balance synergistically. Dual synergy may thus be possible when two drugs affect two different pathways and both unbalance the overall physiological function in the same direction. Thus, with good quantitative data and predictive mathematical models in hand, one may hope to find new therapies that take cellular balances into account and irreversibly and synergistically alter these balances for an intended therapeutic effect.

In microbial infections, as in cancer, the focus has been on the straightforward discovery of synergistic drug interactions. The study by Bollenbach et al. suggests that other aspects of drug interaction are worth exploring, as did their earlier work indicating that antagonistic drug combinations may reduce selection for drug resistance[2] and therefore may be advantageous when the appearance of resistance is a major threat. A general principle may be emerging regarding the effect that nontrivial drug interactions can have on basic global balances in cell physiology. The application of this principle may guide us both in the avoidance of unexpected compensating drug effects and in the design of more powerfully synergistic combinations to treat a range of diseases from microbial infections to cancer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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