Novel patterns for drug synergistic mechanism research

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Abstract

Drug combination based on synergistic effect is commonly used in clinical practice, especially in the application of traditional medicine. Exploring the combination mechanism could help to better utilize this synergistic advantage. However, current research focuses more on the efficacy enhancing of drugs, while ignoring the toxicity reducing effects. Here, we established two drug synergy patterns based on the different situations of drugs and targets, in order to better illuminate the synergistic mechanism of drugs.

Keywords: drug synergy patterns; efficacy enhancing; toxicity reducing; synergistic effect

Citation


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Introduction

In the context of the slowdown in new drugs development, combined medication has become a new attempt [1], and has achieved significant clinical benefits, especially in cancer treatment [2]. The combined use of drugs can produce a synergistic effect, including enhancing efficacy, reducing side effects, and inhibiting drug resistance, etc. The drug synergy involves multiple aspects such as pharmacokinetics and pharmacodynamics, of which pharmacodynamic synergy is more extensive and complex. Researchers are consistently attempting to explore the synergistic mechanism of drugs in the body in order to better utilize this synergistic effect [3]. However, we found that many current studies failing to explain the scientific connotation of drug synergy accurately and comprehensively.

Synergistic effects of different drugs on the same gene (protein, or other target)

This effect includes two aspects: efficacy enhancing and toxicity reducing. The former refers that different drugs act on the same target and exert similar pharmacological effect. These drugs play a “1 + 1 > 2” role through combined use. This is what researchers pay attention to and looking forward to. The latter means that different drugs having opposite effects on the same target. This is often overlooked during research. As shown in Figure 1, we established an innovative drug-gene synergistic regulation pattern, in which the genes are divided into four categories: Efficacy enhancing-Beneficial genes (EEBGs), Efficacy enhancing-Harmful genes (EEHG), Toxicity reducing-Beneficial genes (TRBGs), Toxicity reducing-Harmful genes (TRHG). It should be noted that the function of gene varies in different disease states and body localization, thus the beneficial and harmful function in this model are relative settings. In conventional analysis, it is easy to overlook the changes in the latter two categories. For example, assume that X-gene is harmful, drug A could increase its expression, while drug B could inhibit that. After drug A and drug B work together, they ultimately reduce or maintain the level of X-gene. This pattern is known as TRHGs. For another example, assume that Y-gene is beneficial, drug A could increase the expression of Y-gene, while drug B could inhibit that. After the combined action of drug A and B, the level of Y-gene ultimately does not differ from that before administration. This pattern is known as TRBGs. Researchers often believe that drugs have no regulatory effect on this type of gene because there is no significant change in the expression before and after administration. In fact, if a harmful gene is given to drug A alone, it may cause adverse reactions, which requires the negative inhibition from drug B. If the gene is a beneficial, although administration of drug A could promote its expression, excessive expression may have the opposite effect. Therefore, restriction from drug B is required to maintain the level of this gene at a certain stable state, rather than at an extreme level. On the contrary, drug A could also offset the adverse effects of drug B. Therefore, both above drug synergy modes are meaningful. It can even be said that considering that only a few genes have significant changes after administration (EEBGs and EEHG), while majority of gene levels have no significant differences (possibly belonging to TRBGs or TRHG), the latter two modes may play a more important and fundamental role in drug synergy, as they maintain the overall homeostasis of the body. Recently, artificial intelligence technologies, including machine learning and deep learning, have been widely used in the field of biomedicine. The multimodal synergistic mechanism of drugs can also be evaluated through artificial intelligence to eliminate anthropic omissions and improve analysis efficiency [4].

Synergistic effects of the same drug on different cell types (subtypes, or other targets)

The term “drug synergy” often refers to the synergistic effect of two or more drugs. In fact, the same drug may have diverse synergistic effects by acting on different cells (or subtypes). In addition to the conventional studies in macroscopic indicators, drug synergy may involve multiple dimensions, including synergy between different organs, cells, cell subtypes, organelles, and genes (or proteins). This synergistic effect is also easily overlooked. As shown in Figure 2, we constructed this schematic diagram. Among them, dominant synergy is well-known and expected, while recessive synergy is often ignored since there is no significant difference in gene expression before and after administration. However, although the overall expression of the gene has not changed, this gene may have significant changes between different cell types, and this change ultimately maintains the stability of the body. For example, the overall gene level did not change before and after administration, but the expression of this gene increased in cell X, while decreased in cell Y. Therefore, deeply clarifying the synergistic relationships in different dimensions is conducive to a better understanding of the drug synergistic mechanisms. The rapid development of single cell sequencing technology in recent years has provided new technologies for cell heterogeneity research [5]. Researchers could at least explain the synergistic effects of drugs at the cellular level, including different cell types, different cell subtypes, and so on [6].

In summary, the synergistic effects of drugs have rich connotations, and in addition to efficacy enhancing, attention should also be paid to their toxicity reducing effects. When revealing the synergistic mechanism of drugs, genes that have no significant changes should not be simply ignored [7]. Researchers need to be aware that the synergistic effects of different drugs on the same target, as well as the synergistic effects of the same drug on different targets [8]. These two drug synergy patterns we have established can help investigators better illuminate the drug synergy mechanisms in different situations.

Figure 1: Synergistic pattern of different drugs on the same target (gene or protein). The height of the column represents the relative expression of drug target. According to the pattern, genes (or drug targets) are divided into four categories: Efficacy enhancing-Beneficial genes (EEBGs), Efficacy enhancing-Harmful genes (EEHG), Toxicity reducing-Beneficial genes (TRBGs), Toxicity reducing-Harmful genes (TRHG). M: model group; A: drug A administration group; B: drug B administration group; A+B: combination administration of drug A and B.
Figure 2 Synergistic pattern of the same drug on different targets (cell types or subtypes). The height of the column represents the relative expression of drug target. According to the pattern, synergistic effects were divided into two types: dominant synergy and recessive synergy. Before: before administration; After: after administration.

References