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Mini Review

Development of Combination Targeted Therapies for Multi-Driver Cancers

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ABSTRACT

Most cancers are supported by multiple independent drivers, and cannot be effectively treated by targeted therapies blocking any one driver. Instead, combination targeted therapy which uses a combination of targeted drugs to block all important drivers is required. Developing combination targeted therapies for such cancers requires an understanding of the complex interactions between targeted drugs and the individual drivers as well as other unintended targets. The current pharmacological models, based on the Hill equation, do not adequately describe such complex interactions. This article discusses the general approaches of developing combination targeted therapies, and comments on a recently developed biphasic pharmacological model for characterizing such complex interactions and predicting synergistic drug combinations for multi-driver cancers.

Keywords: Combination targeted therapy; Hill equation; Biphasic pharmacological model; Multi-driver cancers; Protein kinase inhibitors

INTRODUCTION

Targeted cancer therapies use small molecules or monoclonal antibodies to block the function of cancer drivers that is essential for the viability, survival and proliferation of cancer cells. They are most effective toward mono-driver cancers. Successful examples include targeting BCR-Abl in chronic myeloid leukemia, ErbB2 or estrogen receptor in breast cancers, mutated epidermal growth factor receptor in non-small cell lung cancer, and activated c-Kit in gastrointestinal stromal tumors [1-5]. Because cancer drivers are often protein kinases or activate protein kinases, and protein kinases are relatively easy to develop inhibitors for, most targeted therapies are small molecule inhibitors or monoclonal antibodies targeting protein kinases [6-9].

LITERATURE REVIEW

Targeted therapies are effective for mono-driver cancers but not for multi-driver cancers

Despite the dramatic progress in the last few decades, targeted cancer therapies reach only a small fraction of cancer patients. A 2018 study indicates that only 8.33% of all US cancer patients are genomically eligible for targeted therapies, and only 4.9% benefited from such treatments [10]. One fundamental reason for this limited reach is that most cancers are multi-driver cancers, where multiple cancer drivers independently contribute to the cancer cell viability, survival, and proliferation [11-13]. Such multi-driver cancers are intrinsically resistant to any single agent targeted therapy. For a multi-driver cancer, a combination of drugs, each blocking an individual driver and collectively blocking all important drivers, is necessary for effective targeted treatment.

Some targeted drug combinations have been approved for cancer therapy, but effective and synergistic combination targeted therapies for multi-driver cancers remain elusive. A 2017 analysis indicated that most of the benefits of approved combination therapies are derived from different patient subgroups benefiting from different components of the combinations, rather than individual patients benefiting from the synergy or additivity of the combinations [14]. Identifying synergistic or additive drug combinations that specifically target the activated cancer drivers in a multi-driver cancer remains a critical challenge.

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Combination targeted therapies can be developed empirically or by rational design

There are two general approaches of developing targeted combination therapies for cancers: empirical drug combination and rational design. Empirical drug combinations can be formulated by preclinical drug screen of combinations of promising drug candidates or clinical trials of combinations of already approved drugs [15-18]. Empirically formulating and testing drug combinations do not require a precise understanding of the molecular mechanisms of the targeted cancer. It is often hampered by the vast number of possible drug combinations and limited target coverage by the approved drugs. Rational combination design can potentially produce mechanism-based cancer-specific drug combinations for a given cancer, but it requires a mechanistic understanding of the oncogenic mechanisms of the cancer and how the drug candidates interact with the molecular system of the cancer. Such an understanding has been hampered by the unique complexities of protein kinases as cancer drivers.

Protein kinase inhibitors may inhibit multiple protein kinases in multi-driver cancers

At the heart of the challenge is the complex interaction between targeted drugs and potential targets in multi-driver cancer cells. Protein kinases make up one of the largest enzyme families with>500 members in human cells. Due to the structural similarity of these enzymes, protein kinase inhibitors tend to potently inhibit their intended targets, but also invariably inhibit a large number of other unintended protein kinases, albeit with much less affinity. Toward a multi-driver cancer cell, a kinase inhibitor could interact with multiple cancer drivers and protein kinases in other biochemical processes. Thus a targeted drug may have a target-specific inhibition as well as off-target inhibition. When such drugs are combined, the effects become even more complex. Thus, pharmacological and biochemical understanding of the interaction between the drugs and the intended and unintended targets in the cancer system becomes crucial for rational design of combination targeted therapies for multi-driver cancers.

Current pharmacological models do not adequately describe the complex interactions between targeted drugs and the multi-driver cancer system

Currently, pharmacological analysis of how cancer cells respond to drugs is based on the Hill equation (I = Imax X Dn/((IC50*) n+Dn)), which expresses the inhibition (I) as a function of the Drug concentration (D) using three inhibitory parameters: The maximal inhibition at saturating concentration (Imax), the Hill slope or co-efficient (n), and the concentration of a drug that achieves 50% of Imax (IC50*) [19-23]. A simplified version assumes the Imax to be 100% (I = Dn/((IC50) n+Dn), where the IC50 is the drug concentration that inhibits total cell viability by 50%24. The IC50 has been widely used to represent how a drug inhibits cancer cells, such as the Genomics of Drug Sensitivity in Cancer database [24-26].

However, the Hill equation does not distinguish the target-specific and the off-target effects because it is based on the assumption of one drug/one target interaction. Thus it does not adequately describe the complex interactions between a drug and multiple targets in a multi-driver cancer cell. For example, many kinase inhibitors cause unusually shallow dose response curves, suggesting a slow increase in inhibition as drug concentration increases. The classic Hill equation analysis of such shallow inhibition curves results in a Hill co-efficient slope of less than 1, suggesting an apparent "negative cooperativity" [20]. Another study found that 28% of cell response curves are clearly multi-phasic [27]. These dose response patterns likely reflect complex interactions between kinase inhibitors and multi-driver cancer cells, but such complex interactions remain mathematically and mechanistically undefined.

The biphasic pharmacological model can describe the response of multi-driver cancer cells to targeted therapy and help predict mechanism-based drug combinations.

To characterize the interaction, we recently examined how a panel of approximately 20 lung, leukemia, colorectal cancer, and triple negative breast cancer cells responded to a panel of kinase inhibitors [19,28-30]. We discovered that these cells can be divided into mono-driver cancer cells and multi-driver cancer cells. While the mono-driver cancer cells, CTV-1 (acute myeloid leukemia) and HCC-827 (non-small cell lung cancer) respond to inhibitors to the main driver in a manner conforming to the Hill equation, most colorectal cancer and triple negative breast cancer cells are multi-driver cancer cells [19,28,29,30]. They are inhibited by multiple kinase inhibitors in a shallow or biphasic dose response pattern. These responses can be described by a biphasic model (I=F1x[D]/([D]+Kd1)+F2x[D]/([D]+Kd2))[19,30]. In this model, the inhibition (I) by a drug has two phases: F1 and F2, as fractions of total cell viability, and each phase has its own binding affinity (Kd1 and Kd2). Fitting the dose response data to the biphasic equation yields three inhibitory parameters, F1/F2 ratio, Kd1 and Kd2.

This analysis suggests that a multi-driver cancer cell responds to a driver inhibitor in the following manner: The inhibitor causes a partial inhibition of cell viability (F1) by blocking one of the drivers with high affinity (Kd1). As the drug concentration increases, it causes additional off-target inhibition (F2) with much lower affinity (Kd2). This mechanistic understanding predicts that the combination of two or more such inhibitors with independent F1 inhibition would potently and fully block the cell viability by each inhibitor blocking an independent driver. In numerous cancer cell models, this approach helped identify highly effective and synergistic combinations of targeted drugs. Such combinations often achieve combination indexes far below 0.1, which translate to combination dose reductions far greater than 10-fold [19,30]. Molecular analysis of the effects of the individual drugs and drug combinations confirmed that each inhibitor independently blocks its intended target and the combinations block multiple activated signaling pathways [19,30]. These results provide a promising approach toward rationally designing mechanism-based combination targeted

therapies for multi-driver cancers. If further validated in animal models and clinical settings, the rationally designed and mechanism-based combination targeted therapies would likely expand the reach of targeted therapy to most, if not all, cancers.

CONCLUSION

In summary, developing combination targeted therapy for multi-driver cancers is a complex challenge and will largely determine if targeted therapy will remain a niche option for a small fraction of cancer patients or a widely beneficial treatment for most if not all cancers. The biphasic analysis-based rational design is a promising approach for developing combination targeted therapies for multi-driver cancers, but its full potential remains to be determined.

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