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Commentary

Proteomic research and protein biochemistry for targeted therapy of anti-cancer drugs

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Abstract

Despite the advancements of medical care and pharmaceutical technologies, unfortunately in recent decades, epidemiological surveys have identified that the population of cancer patients are indeed increasing in multiple regions. So, cancers go on threatening human health and life to a larger and larger extent. A series of special anti-cancer drugs are known as "targeted therapies". Those anti-cancer drugs work through blocking bioactivities of specific onco-gene or onco-protein so as to prevent the progressions of cancers. Nevertheless, due to the genetic properties of cancers are highly heterogeneous and complex, the anti-cancer therapeutic mechanisms of those drugs are yet fully known. Consequently, those anti-cancer drugs of targeted therapies are only effective for a limited part of cancer patients. Therefore, it is urgent and necessary to study and reveal the full mechanisms that how anti-cancer drugs of targeted therapies are working *in vivo*. Given that proteins, or proteomes, are the direct effectors of most physiological functions, it could be interesting to study the working mechanisms of anti-cancer targeted therapies from the perspective of proteins and protein biochemistry. To this end, recent research works were selected to introduce how interplay between proteins and anti-cancer targeted therapies were studied, both in pros and cons. Through reviewing these research works, insights of proper and promising research and development paradigm of protein and proteomic researches for precision anti-cancer targeted pharmacotherapies were summarized.

Keywords: Cancer targeted therapy, High throughput sequencing, Protein biochemical research, Proteomics, Post translational modifications, Precision medicine, Precision oncology

Main Text

Cancers are known to be serious threats for human health and life. One large difficulty of diagnosis is that several types of cancers display no obvious phenotypic signs in the early and middle stages. Therefore, when those cancers are diagnosed, they are usually in late stages, and hence are difficult to treat due to complicated factors, such as, metastasis, and drug resistance.

Recent years, thanks to collaborative effectors of different research fields' scientists and researchers, targeted pharmacotherapies have been developed for specific types of cancers. Such pharmacotherapies are one class of anti-cancer drugs targeting specific product protein of cancer driver gene with specific mutations (Briefly, such anti-cancer pharmacotherapies are referred as Targeted Anti-cancer Pharmacotherapies, or TAPs, in later texts). Such drugs have been approved by drug regulatory agencies and available to patients now. TAPs work through binding or inhibiting the activities of proteins stimulating the progression of cancers. Hence the progression of cancers could be hindered or slowed down. In such way, parts of cancer patients whose tumorigenesis is driven by those specific mutations of specific oncogenes, could live for longer time when target therapies are appropriately used for anti-cancer treatments. Notably, such onco-proteins are also mutants usually, i.e., they are the translated and synthesized products from those mutated cancer driver genes (or called onco-genes).

For example, the United States Food and Drug Administration has proved the sotorasib and adagrasib, which are able to treat a part of Non-Small Cell Lung Cancer patients carrying the mutated *KRAS* gene and mutant protein KRAS G12C [1].

Nonetheless, not all patients can benefit from targeted therapies. In fact, TAPs, including aforementioned example anti-cancer drugs, only work for a limited part of patients with specific onco-gene mutation. Yet, the vast majority of patients harboring the same onco-gene mutation do not have good drug response to these anti-cancer targeted therapies, which remains to be a great pity. And nobody knows why because how TAPs work *in vivo* are not fully investigated and hence the molecular and physiological mechanisms of actions of TAPs are not well understood.

For example, currently, in order to identify whether cancer patients can be treated with specific kind of TAPs, it is required to test whether patients have specific onco-gene mutations targeted by TAPs. And such molecular subtyping processes currently only rely on high throughput sequencing technologies (also known as Next Generation Sequencing). However, as mentioned above, TAPs usually work via binding and interacting with onco-proteins, rather than directly working on genes.

Here, a critical important basic fact to bear in mind is that, since the regulations of DNA transcriptions, RNA translations, peptide synthesis, protein Post-Translation Modifications (PTMs) and other biological/physiological processes *in vivo* are highly complex and complicated, ***it is no guarantee that mutated genes will trigger high expression of relevant mutant proteins in vivo.*** This rule is surely applicable to any organisms, of course including those healthy people and patients, as the regulations of DNA transcriptions, RNA translations, protein post-translation modifications (PTMs) and other biological/physiological processes are highly complex and complicated. Consequently, such complex uncertainties between mutated gene and relevant mutant protein expression give rise to large uncertainties of whether TAPs work or not on specific individual patients despite a great number of cancer patients are harboring the same specific mutations targeted by TAPs.

In order to let more patients benefit from those TAPs, it is urgent and necessary to investigate the reasons why TAPs only work on limited part of patients. One wise and important way to go is of course studying those proteins targeted by and interacted with TAPs, as proteins are known to be the main functional biomolecules and effectors *in vivo*. E.g., proteins are extensively involved in diverse kinds of *in vivo* biochemical reactions, immunological responses, and molecular signal transductions in broad sorts of biological and physiological processes. Specifically, in order to characterize how targeted proteins interact with TAPs, several important aspects, such as the mutation information in amino acid level, 3D structure conformation, binding sites, expression level of those targeted proteins, should be paid attention to and elaborately investigated, since high throughput sequencing technologies are not able to obtain above valuable information of proteins.

In light of the above ideas, scientists started to explore proteins or proteomes' interactions with TAPs. To take Liu at al.'s work as an example [2], which used multi-omics technologies to systemically characterize genomic, proteomic, and phospho-proteomic landscape of KRAS mutants in different cancer cell lines from different tissues. Specifically, Liu et al. combined and integrated the genomic signature information, pathway enrichment information, proteomic landscape, and phospho-proteomic landscape, so that Liu et al. were able to obtain all necessary multi-omics information and finally were able to identify and propose potential pharmacotherapy for a subset of *KRAS* mutant cancer.

Aforementioned Liu et al.'s work is a good example demonstrating that, in order to systemically study and characterize the molecular mechanisms of TAPs, the full landscapes of gene expressions and regulations are necessary. I.e., it is necessary to access genomic information, mutation information, proteomic information and even that proteomic information of PTMs due to the super high complexity in gene and protein regulatory processes. Again, none of any kind of information can be ignored if researchers aim to conduct a systemic and sound proteomic or protein study regarding TAPs.

However, without paying attention to the above important knowledge and rules, research can easily be guided to wrong ways. In contrast with Liu et al.'s work [2], a recent published work by Zhan et al. showed wrong guidance and example for studying TAPs and clinical drug targets of cancers [3]. Briefly, Zhan et al. conducted comparative experiments to clinical cancer samples with diverse kinds of cancers and with imbalanced sample sizes. Zhan et al.'s work compared number of actionable mutated genes detected by sequencing technology versus number of United States Food and Drug Administration-approved clinical drug targets detected by mass spectrometer [3]. And then, they claimed that mass spectrometer-based assays could provide more cancer treatment options than sequencing technology-based assays did [3]. Finally, Zhan et al. concluded that protein overexpression is a potential indicator for guiding TAPs [3].

Zhan et al.'s work and published paper are problematic in multiple points [3]. First and foremost, Zhan et al.'s work had low integrity in source data and test samples. Such low integrity leads to questions and concerns about reliability and validity of their experimental results. Second, Zhan et al. forgot that current TAPs are based on only gene mutation information, rather than the expression level of targeted proteins. Obviously, so far, getting gene mutation information can only rely on sequencing technologies. Instead, those usual assay protocols of mass spectrometer-based proteomic assays can only quantify the expression level of proteins but cannot access the mutation information of proteins. Are there assay protocols for mass spectrometers to detect and obtain mutation information of proteins? There may exist such rare and special mass spectrometer-based assay protocols, but it must be rare since elaborated efforts in modifying and optimizing protocols from those usual protocols are required. Hence, most mass spectrometry laboratories would not be able to set up and run such assay protocols, given that such rare assays are highly costly and expensive. Importantly, going back to in Zhan et al.'s work [3], at least they just ran those usual protocols for quantifying protein expressions, and they did not even run assay protocol for detecting the most commonly seen PTM information --- the phosphorylation information of proteome. On the contrary, as mentioned above, Liu et al. has made efforts to access those phospho-proteomes, because it is commonly known that PTMs affect the confirmation of proteins. Confirmation of protein determines the binding and interaction with drugs, and hence affect the generation of therapeutic effects. Thus, PTMs affect proteins' binding and interactions with drugs in great extent as well, as demonstrated in Liu et al.'s work [2]. That's why the experiment designs, workflow, methodology of Liu et al.'s work can be seen as a correct and model example [2], while Zhan et al.'s work cannot [3]. To sum up the third viewpoint of mine, Zhan et al.'s work ignored the important roles of PTMs for target proteins and did not conduct experiments to check proteins' PTM information. I.e., Zhan et al.'s usual proteomic assays

for just simply quantifying protein expressions had little reference value for either guiding anti-cancer clinical treatment options or studies of TAPs.

Fourth, Zhan et al. also claimed their *in vivo* experiment using mouse model and Map2k1 worked well and could support their viewpoint. But evidence supporting Zhan et al.'s conclusion of protein overexpression indicator was quite weak and in low confidence level [3]. Zhan et al.'s *in vivo* experiment with low sample number and merely single target are not persuasive, because initially, Zhan et al. work on single protein of Map2k1 proved nothing since their conclusion did not limit on that single protein. Instead, they intended to extend and apply their conclusion to diver kinds of clinical drug targets, as they have written in the manuscript in obvious way. That's why their conclusion is highly problematic and unreliable. Moreover, the reproducibility of Zhan et al.'s *in vivo* experiment should be questioned. If Zhan et al. want to prove their conclusion, they are required to provide evidence with high confidence. E.g., they should screen a lot more drug targets using a lot more numbers of mice, rats, or organoids.

Last but not least, Zhan et al. recommended that clinicians could adopt their hypothetical protein overexpression-based therapeutic guidance for treating cancer patients in the real world [3]. Obviously, adopting such highly unreliable therapeutic hypothesis is putting people in great risks, both for clinicians and patients. Adopting such unreliable medication strategy could let cancer patients suffer from side effects induced by drug but without knowing whether that drug can benefit patient or not. For clinicians, doubtlessly, adopting such risky medication strategy leads to unknown outcomes of healthcare quality and is inconsistent with guidelines and ethics of clinical practice. And thus, it is putting clinicians' career in great risks as well.

In summary, functional and physiological roles of proteins, especially those proteins targeted by TAPs, are of high importance and significance for investigation. It is one of the good ways to explore and identify full therapeutic mechanisms of TAPs. And due to the high complexity of biomolecules themselves and those relevant *in vivo* biological regulatory processes, researchers who want to shed lights on clinical therapeutics should pay attention to multiple properties of biomolecules, such as aforementioned PTMs, mutations, structure conformations of target proteins.

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