



CLINICAL GROUP

Received: 15 September, 2022

Accepted: 26 September, 2022

Published: 27 September, 2022

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Opinion

Bio-informatics approaches in liver disease: Incomplete without experimental validation

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Abstract

In the search for the treatment of hepatic diseases, multiple approaches have been used frequently such as bioinformatics and algorithm-based systems biology for the screening of already published data that leads to the identification of promising drug candidates at molecular levels. These studies provide a large data set of information and claim to identify many genes, which could be targeted for the cure. However, it is important to note that the identified compounds are only predictions and the potential of these suggested molecules or genes should be well confirmed by adopting robust and critical experimental approaches to satisfy all possible aspects to use them safely for therapeutic purposes. Therefore, I put forward the opinion that these predicted markers whether prognostic, diagnostic, or molecular must be evaluated critically through a well-defined experimental pipeline.

Introduction

Hepatocellular Carcinoma (HCC) is one of the most devastating liver diseases. It has high heterogeneity and poor prognosis making it the second most dangerous cause of mortality in comparison to other cancers. It happens mostly with people suffering from chronic liver diseases such as liver cirrhosis caused by hepatitis B and C viral infections.

The diagnosis and treatments are still very limited for such diseases including blood tests, CT scans, MRI, or invasive tests (liver biopsy). Liver biopsy has the gold standard to achieve the best diagnosis of liver-related diseases. Treatment options depend on the size and stage of the tumor including curative resection, liver transplantation, radiofrequency ablation, trans-arterial chemoembolization, radioembolization and systemic targeted agent like sorafenib.

The exponential growth in using bioinformatic and systems biology approaches leads to the expectation of interpretation of large data sets by developing algorithms. However, clinical relevance, data validation and reproducibility of such data are still a concern. Moreover, the meaningful discoveries hidden in

extensive data analysis could be useful for drug discovery and the repurposing of drugs.

Results and discussion

As mentioned above liver disease is always a concern to human health however the research should indeed lead to the solution of a cure for the disease. In the current article, two such studies have been considered to discuss where the authors either used an experimental approach [1] or developed a computational algorithm after analyzing already published data to find out a few potential targets for diagnosis and cure [2]. Although we may smartly use computational modeling methods to screen large data sets and identify novel targets, it should carefully be validated through a robust experimental pipeline including in vitro and in vivo models before moving to the clinics. Here the opinion has been explained by taking the example of these two published articles.

A recent article published in Science [1] showed a novel type of programmed cell death induced by copper also known as cuproptosis. Authors have revealed the lipoylated TCA (Tricarboxylic acid) cycle proteins (dihydrolipoamide



S-acetyltransferase, DLAT) were targeted by excess accumulation of copper. This mechanism further leads to proteotoxic stress and forms a new type of cell death i.e cuproptosis. Copper is an important co-factor for enzymes across the animal kingdom and copper ionophores and chelators have been demonstrated as an anti-cancer agent. Therefore, the study has presented an essential paradigm of limited concentration of components such as a small intracellular concentration of copper can lead to cell death. They have investigated the protein lipoylation mechanism behind copper-induced cell death. In the mammalian system, a limited number of proteins are known to be lipoylated following being concentrated in the TCA cycle and performing the enzymatic function. Moreover, the study describes the connection between excess copper-mediated cell death and mitochondrial metabolism including acute proteotoxic stress. Further checked the lipoylation and Fe-S cluster moiety in human cancer cells [3]. Copper ionophore, elesclomol has shown anti-cancer activity in phase 3 clinical trials with low LDH levels. Low LDH represents high mitochondrial metabolism dependency which suggests sensitivity to copper ionophore correlating with high lipoylated TCA enzymes. Notably, they found a high correlation between FDX1 and lipoylated proteins in various human tumors suggesting that copper ionophore can be used as treatment with a biomarker-driven approach.

The above study has demonstrated clinically relevant research which has been proven by various experimental approaches and further elaborated the mechanism that is suggesting the ancient copper homeostatic mechanism.

On the other hand, a recent article in frontiers in immunology [2] predicted the role of cuproptosis in HCC. By using a set of bioinformatic tools, showing that FDX1 and cuproptosis-related other genes are regulating HCC and FDX1 could be a good prognostic marker for HCC. They have used the cuproptosis concept from the above-mentioned publication in science and looked for the involvement of cuproptosis in HCC as the liver is the main organ for copper metabolism. Liver cirrhosis has been shown to accumulate copper. The study is based on the available data from the cancer genome atlas (TCGA) and analyzed by scoring bioinformatic tools. Their first statement was that FDX expression was lower in HCC samples vs healthy liver tissue found by the TCGA database. However, the importance of the FDX gene in HCC has already been established experimentally in 2017 [4]. Nevertheless, they further used LASSO for FDX 1-related genes that were reduced in the HCC samples, predicting that the crucial four genes regulate the metabolism and have a function in tumor development and progression. Further, indicating the response of immune cells by quoting that HCC patients with high CRRS exhibited more pro-tumorigenic response rather than anti-tumorigenic response. However, the relevant point that cuproptosis-inducing drug affects the function of anti-tumor immune cells and components of the Tumor microenvironment (TME) have not been discussed. Lastly, all the predictions by authors suggest/indicate that future studies of combined therapies inducing cuproptosis may lead to improve the prognosis of the disease (HCC).

Although, both the studies presented the importance of cuproptosis in liver disease the validated and proven facts can be seen only by the experimental studies where the first study [1] clearly showed the mechanism behind the cuproptosis by checking the aggregation of lipoylated proteins. Conversely, none of the above predictions was validated by any experimental presentation in the second study [2]. Experimental models are always crucial for proving the hypothesis. We must focus on the experimental validation of the predicted results obtained from the bioinformatic approach. These approaches can lead us to predict various useful proteins or mechanisms behind the process but ultimately their therapeutic potential should be checked critically through a well-defined experimental pipeline and answer the key biological questions. Therefore, I strongly suggest to follow the combinatorial approach including the prediction and validation of therapeutic molecules.

Conclusion

This article strongly supports the idea of experimental models however the limitation of the bioinformatic approaches can be neutralized either by adopting experimental validation or by focusing the multi-OMICS approaches such as RNAseq, proteomics, or metabolomics [5]. These recently developed techniques provide us with a global snapshot of genome expression during the disease process. For example, RNAseq/proteomics from HCC patients vs healthy samples includes the transcription or translation data of genes upregulated/downregulated in disease vs healthy. This large data can be very important and useful for diagnosis and treatment in addition to the bioinformatics and systems biology tools.

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