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Knowledgebase for addiction-related genes: Is it possible an extrapolation to rational multi-target drug design?

L. Michel Espinoza-Fonseca

Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, MN 55455, USA
Departamento de Bioquímica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala, Mexico City 11340, Mexico

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ABSTRACT

In recent years the *single-probe–single-target* approach in drug design has started to be smoothly replaced by the *single-probe–multiple-target* (or multi-target) one, where a single drug is able to tackle different, but disease-related targets in a selective manner. However, the design of multi-target drugs has been hindered by a lack of a systematic network of disease-related common pathways. The recent development of the knowledgebase of addiction-related genes (KARG) has provided important hints on how to rationally design multi-target probes by connecting experimental techniques with available network models. In this perspective, the use of KARG as a template to build knowledgebases of disease-related genes for the rational multi-target drug design is suggested. Moreover, it is proposed that building knowledgebases of disease-related genes will become a necessary and ubiquitous tool in the rational design of multi-target drugs.

1. Tackling one is not enough: the multi-target drug approach

Drug discovery efforts in the past several decades have followed the *single-probe–single-target* approach; however, researchers in the drug discovery field have realized that communication mechanisms within the cell are arranged as robust, highly cooperative networks, which consist of complex nodes that interact through weak and strong links.[1–4] These links play a key role in the regulation or control of a given biological phenomenon. Moreover, cellular networks often possess buffering mechanisms that prevent major perturbations despite single drug-induced significant changes in one of their constituents.[5] On the basis of these observations, in recent years the *single-probe–single-target* approach in drug design has started to be smoothly replaced by the *single-probe–multiple-target* (or multi-target) one, where a single drug is able to tackle different, but disease-related targets in a selective manner.[6–10] Such approach hast started to be applied to neurodegenerative[11–16] and psychiatric diseases,[17–19] cancer[20–28], and the development of anti-oxidant agents.[29]

To date, the design multi-target drugs has significantly relied on serendipitous discovery of probes[6], the application of molecular descriptors and structure–activity relationships for target-selective ligands[30] and the use of network models.[5,31–34] Although these techniques have proven to be of great utility in the discovery and design of new multi-target drugs, they are of limited utility if a comprehensive description of disease-related molecular networks and their targets is not available. Current experimental efforts in designing multi-target probes are limited to trial-and-error assays on a few number or targets that presumably play a significant role in the disease, while promising network models cannot be effectively applied due to the absence of systematic disease-related molecular pathways. Hence, the need for a complete topological description of molecular networks is essential to achieve synergism between state-of-art experimental and computational techniques. Considering the above, a question arises: What would be the starting point to create a complete description of disease-related molecular networks for the rational design multi-target drugs? A recent study on the systematic building of a molecular database for addition-related genes[35] might be the answer to this question.

2. Knowledgebase of addiction-related genes: a molecular network of common pathways

'Is there a common molecular pathway for addiction?'[36] was the question that inspired Wei and co-workers to construct a systematic database of addiction-related genes, also known as *knowledgebase of addition-related genes* (KARG).[35] By systematically and statistically analyzing a total of 1500 human addiction-related genes, the authors identified 18 enriched molecular pathways directly related to addiction. Furthermore, the authors found that five out of eighteen molecular pathways were common in four types of addictive drugs (alcohol, nicotine, cocaine and opioids). Although three out of the five proposed common pathways were

E-mail address: mef@ddt.biochem.umn.edu

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previously linked to addictive behavior, two other common pathways which were not previously linked to addiction were identified. Furthermore, the authors noted that real systems are dynamic and include wide-ranging crosstalk (links) among functional modules (nodes). These five common pathways were connected into a hypothetical common molecular network for addiction, showing that fast (signal transduction) and slow (transcription and translation) positive feedback loops were interlinked through the calcium/calmodulin-dependent protein kinase II. The authors concluded that fast and slow positive feedback loops interlinked with calcium/calmodulin-dependent protein kinase II may provide insightful information to explain some of the irreversible features of addiction.[35] These exciting results have shed new light on how to clinically manage the addiction to abusive substances in humans.

3. Systematic knowledgebases in multi-target drug design: is it possible an extrapolation to multi-target drug design?

Effective design of multi-target probes has been hindered by the lack of a systematic knowledgebase of disease-related targets. The building of KARG has shown that it should be possible to merge common molecular pathways into a knowledgebase of disease-related genes. Furthermore, KARG has proven to be a powerful tool in the topological and dynamic description of the complex network of addiction-related genes. Thus, the idea behind KARG can be effectively extrapolated to multi-target drug design by conceiving a dynamic *master* network constituted by pathways (tightly coupled sub-networks). The minimal functional element of each pathway may be a receptor or an enzyme. Communication within and between pathways is given through links (i.e., the degree of coupling between two elements of the network). At the same time, each pathway is also a node of the *master* network; each pathway may communicate to each another through either *weak* or *strong* links.[1,5] By introducing the concept of *weak* and *strong* links into the knowledgebase, the intrinsic dynamics of the network are taken into consideration.[37] Such idea can be easily adapted to multi-target drug design in order to create a dynamic topological description of a given disease. Selection and sorting of disease-related genes will constitute the core of the nodes of the knowledgebase network, while statistical analysis would provide a quantitative measurement of the degree of coupling between each pathway and their individual receptors. The knowledgebase will not only provide information on the pathways and their targets involved in a given disease, but also on how those pathways can be efficiently and systematically knocked-out by a single probe in order to produce the desired therapeutic effect.

4. Integrating common molecular pathways: toward the rationalization of multi-target drug design

As an example of how a knowledgebase of disease-related genes can be built, breast cancer may be considered as a study case: There is an extensive database of breast cancer-related genes, which contains 2958 associated genes.[38] This database can be converted into a knowledgebase of breast cancer-related genes by using a similar approach employed by Wei and co-workers.[35] Moreover, a database of therapeutically relevant pathways is available,[39] which can be used to facilitate the building of the knowledgebase. In order to quantitatively evaluate the degree of coupling between breast cancer-related pathways, hypergeometric distributions and statistically significant correlation values may be calculated.[35] By integrating this information in a comprehensive knowledgebase, a complete and systematic network of breast cancer-related genes would enormously facilitate the tracking of relevant druggable targets and the subsequent improvement of current treatments.

It is necessary to emphasize that knowledgebases of disease-related genes should not be considered as a mere topological description of the interlinked pathways; instead, knowledgebases should be treated as continuously dynamic 'master-networks'. In this respect, inspiring work by Csermely and co-workers on the use of network analysis in multi-target drug design has provided important hints on the quantitatively understanding of complex biological networks.[5] By classifying links between nodes as *weak* and *strong*, Csermely and co-workers have introduced a concept that will be critical for comprehension of multi-factorial diseases at molecular level. Moreover, pathway analysis can be used to synergize the efficacy or suppressing individual side effects of multi-target drugs.[31]

By making such knowledgebases available to researchers in the field of medicinal chemistry, novel approaches could be used to rationally develop multi-target drugs. For instance, if one knows that *N* druggable targets within the knowledgebase of breast cancer-related genes may significantly play a role in the development of the disease, fragment-based[30,40,41] and multimeric-drug[42] approaches can be used to design probes that selectively bind to those targets. Simultaneously, by knocking-out multiple but key targets, the therapeutical efficiency would be significantly improved.[5,43] Additional technologies, such as Target Informatics Platform (TIP), a novel structural informatics approach for amplifying the rapidly expanding body of experimental protein structure information, can speed up the discovery and optimization of multi-target drugs on a genomic scale. In TIP, structural information is augmented by using homology modeling and targets' binding sites are systematically compared.[44] Furthermore, to assess the efficacy of these multi-target drugs, in vivo pharmacology might become important again.[2,5,45] In order to achieve an optimal in vivo testing, better animal models are needed. Better animal models can be achieved by 'humanizing' the metabolism and signaling of test animals. Disease target genes and their protein products might be transformed from drug targets to core elements of better animal models in the future.[2,5] By integrating these technologies into knowledgebases of common molecular pathways, the selectively promiscuous behavior of single probes would be efficiently achieved. In the near future, such integrated approaches would constitute the backbone of rational multi-target drug design.

5. Concluding remarks

Recent advances in the field of drug design have shifted the *one-probe–one-target* philosophy to a *one-probe–multiple-target one*. However, despite the availability of state-of-art experimental and computational screening techniques, rational design of multi-target probes has been hindered by the lack of a systematic database of drug gable targets. In this perspective, it is proposed that building knowledgebases of disease-related genes will become a necessary tool in the rational design of multi-target drugs. Moreover, the use of network models in such knowledgebases will provide a quantitative description of the dynamical networks involved in a disease.

Quantitative and qualitative analysis of a multi-factorial disease will be helpful not only for the rational design of highly selective drugs for multiple targets, but also for the discovery and understanding of new disease-related pathways. New emerging approaches, such as game theory-based and learning models earning and innovation may help to understand the re-organization of biological networks.[46] By integrating such approaches, knowledgebases of disease-related genes will be continuously

enriched and updated, allowing medicinal chemists and pharmacologist to rationally improve the efficiency of multi-target drugs.

KARG has already proven to be a useful approach that can be extrapolated to multi-target drug design. Thus, it is not hard to imagine that in the near future knowledgebases of disease-related genes will become an essential and ubiquitous tool in the rational design of effective multi-target drugs.

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