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Editorial Open Access

Targeting the Diseasome Complexity with Natural Sources

Alexandra Koutsotoli[1] and Andreas G Tzakos[2]*

[1]Department of Hygiene and Epidemiology, Medical School, University of Ioannina, Greece
[2]Department of Chemistry, University of Ioannina, 45110, Ioannina, Greece

Drug targets do not function in isolation; on the contrary, they operate in a concerted and coordinated way through developing interactions with multiple partners, forming a complex interaction network, the so-called interactome. This interaction network is not rigid and invariable, but is constantly altered and reshaped, conforming to the pliable signaling responses of a living organism. In a healthy condition, the content of these interactions although of their inherent dynamic nature, is spatiotemporally conserved. Once this dynamic interaction network is perturbed on its content, localization and the temporal organization of interactions, a disease pathophenotype emerges.

The disease condition is normally characterized by the development of a higher degree of biomolecular interactions, with respect to the non-disease state [1,2]. Due to the enhanced interaction capacity of the disease state, cross-talking among different diseases exists. Indeed, it has been recognized that perturbations caused by one disease can affect other disease modules [1,2], formulating the concept of the diseasome. The diseasome represents network maps on which the nodes are diseases and the links are molecular interconnections between disease-associated cellular components [1,2]. Decoding the architecture of the network maps, characterizing a disease condition could uncover better targets for drug development as also more effective disease biomarkers.

In order to re-establish the original balance (healthy condition/cure) in the interaction network, more than a single interaction/link should be restored. However, drug development is largely hampered in variable environments due to the inherent dynamic nature of the original interaction network (healthy state), as also the pliable behavior of the diseasome. Systematic efforts to increase the coverage of human interactome maps [1,2] provide a global understanding of diseases, in the context of network principles and allow decoding of fundamental properties of genes involved in disease. Besides this accumulated knowledge and continuous flow of information, numerous key questions persist. How can we design drugs that will be capable to disrupt specific interactions on the interactome map and allow a re-establishment of the dynamic balance on the interaction network? If intrinsic protein disorder will be incorporated in this scheme with which most of the proteins implicated in diseases are empowered, then how can we perform rational structure-based drug design?

A first approach to develop drugs for such diverse targets is to synthesize a large array of compounds, so as to cover large proportions of the chemical space. Indeed, utilization of probabilistic approaches (CombiChem) to screen thousands of compounds against a single target have been dominant in recent drug development [3]. Unfortunately, these approaches were followed in several instances with high attrition rates in drug development. This may happen simply since, chemical universe is just vast and may contain up to 1060 molecules. Instead of increasing the content of the chemical space for the candidate molecules, a more efficient approach could be to map the sub-portion of the chemical space that is of biological relevance. Natural products have been evolutionarily selected after nature's combinational chemistry to interact with multiple biological target molecules. They also frequently resemble biosynthetic intermediates or endogenous metabolites and thus, can favorably utilize native active transport mechanisms [4]. Thus, natural products could form a framework for effective screening of the part of the chemical space that is of biological relevance.

Interestingly, although the pharmaceutical industry has historically relied on 'druggable' proteins for drug development, most FDA-approved drugs were developed in the absence of any information of the molecular mechanisms responsible for their indicated diseases, as also the pharmaceutical target [1,5]. Charting the origin of the New Chemical Entities (NCEs) launched onto the market between 1981 and 2002 illustrated that natural products or natural product-derived drugs comprised 52% [6]. Furthermore, natural products have been used to treat 87% of all categorized human diseases [7-9]. Therefore, natural products provided a solid basis for the development of new drugs, as also efficient lead compounds for further drug optimization. The inherent drug-likeness presented by natural products is based both on their privileged structural diversity, as also their functional diversity and adaptation within the interactome due to their elaboration within living systems and thus, optimization to participate in molecular recognition [4,10]. For instance, the microcystin biosynthesis gene cluster, mcyS, responsible for the synthesis of the natural product microcystin, is comprised of at least 10 different genes [11]. It is, therefore, evident that natural products are optimized to interact with diverse biological systems [12].

Plants are rich sources of natural products. Breakthrough in structure determination as also in separation technologies, have reduced the difficulties in screening mixtures of complex molecules [4,13-18]. Triggered from the diverse nature of natural products present in complex plant extracts, we recently studied their effect on complex biological systems. For instance, we recently monitored the anti-proliferative activity of Rosmarinus officinalis and Salvia officinalis extracts against cancer cells and correlated this activity with their phytochemical profiles, using LC/DAD/ ESI-MSn and NMR spectroscopy [15]. Both extracts exerted cytotoxic activity through dose-dependent impairment of viability and mitochondrial activity of rat insulinoma m5F (RINm5F) cells. Reduction of RINm5F viability was mediated by nitric oxide (NO)-induced apoptosis. These extracts potentiated NO and TNFa release from macrophages, therefore, enhancing their cytocidal action. The recorded potentiation of immune cell function by these extracts is of great importance for the future development of potential anticancer therapy. On the basis of the analysis of the phytochemical profile of the two extracts, we determined that the rosemary extract developed more pronounced antioxidant, cytotoxic and immune modifying activities, with respect

***Corresponding author:** Andreas G Tzakos, Department of Chemistry, University of Ioannina, 45110, Ioannina, Greece, E-mail: atzakos@cc.uoi.gr

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to the sage extract, probably due to the presence of betulinic acid and a higher concentration of carnosic acid in its phytochemical profile.

In another study, we aimed for natural compounds that could be potent to thrombogenesis [19]. Thrombogenesis is a complex pathophysiological process, and platelets are the key players in arterial thrombosis. To combat perplexed pathophysiological process such as thrombogenesis, multi targeted drugs should be developed. Betulinic acid, found in the bark of several species of plants, confers a promising multifunctional compound that targets multiple steps in signal transduction pathways. It has been found to illustrate numerous pharmacological actions including anticancer, antiinflamatory, antimalarial etc. On the frame of this study, we found that betulinic acid is very potent in inhibiting platelet activation induced by three different agonists [19]. We also defined the existence of a common chemical space sampled between betulinic acid and approved antithrombotic drugs, further strengthening the fact that natural compounds could be used to target complex pathophysiological diseases.

The activity of plant extracts and specifically the herbal tea from Sideritis clandestina subsp. clandestina was also tested on the behavioral and oxidant/antioxidant parameters of adult male mice [14]. The neurotoxic effects of oxidative stress and the consequent neurodegeneration in specific brain areas have been proposed as causal factors in Alzheimer's disease, Parkinsonism and aging process. We found that Mountain tea drinking prevents anxiety-related behaviors and confers antioxidant protection to rodent's tissues in a region-specific, dose-dependent manner [14]. This study further supported the judicious role of natural derived products in the prevention of neurobehavioral diseases and the deleterious effects of aging.

The past few years have witnessed systematic efforts to chart in a more concrete way, the human interactome maps as also to exploit the network-based dependencies between pathophenotypes and their disease modules. Such studies shed light on the complexity of multifactorial diseases, indicating that efficacious therapies will require altering entire pathways, rather than single proteins. An important source of compounds for targeting the biologically relevant chemical space of complex diseases could be achieved through natural products. Natural products have been evolved through natural selection to interact with multiple targets and to modulate multiple signal transduction pathways. A future understanding of the diseases in the context of network principles, could address some fundamental properties of the genes that are involved in disease. In addition to this, exploring the mechanism behind the effective multi-targeting profile of natural products could also offer a more effective network-based drug design framework, to target the complex diseasome.

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