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Perspectives on Computational Structural Bio-Systems

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Abstract

Non-molecular systems biology is aimed at the prediction of the functional features of bio-systems on the basis of known cell proteomes and interactomes. Understanding the interactions between all the involved molecules is therefore the key for gaining a deep understanding of such processes. Albeit many thousands of interactions are known, accurate molecular insights are available for only a small fraction of them. The difficulties found in the resolution of atomic level structures for interacting pairs, make the predictive power of molecular computational biology methods essential for the advancement of the field. Indeed, bridging the gap formed due to the lack of structural details can therefore transform systems biology into models that more accurately reflect biological reality.

Introduction

Molecular biology, in the genome era, does not refer to studies involving just single macromolecules, it actually involves the study of complete cellular pathways, and why not, even entire organisms. Indeed, the world-wide genome-sequencing projects revolutionized the field and are producing unimaginable amount of biological data, providing a near complete list of the components that are present in an organism. Furthermore, the post-genomic projects that have the main scope of offering the scientific community with the relationships between all these components, are giving more and more data, not always of high quality.

A natural consequence of the outcomes of these large efforts was the birth, several years ago, of the "Systems Biology" field, mainly devoted to the unraveling and understanding of metabolic and signaling pathways or gene-regulatory networks. Systems biology relies on a detailed knowledge of protein–metabolite, protein–protein and protein–nucleic-acid interactions at the cellular level. In this regard, it is also important to take into account that, at the very bases, all of these processes involve molecular recognition: for example the process by which two or more molecules interact to form a specific complex. Albeit far from being completely characterized [1], the complex formation processes are surely dominated by short-range, often transient, interactions at the contact surface of the molecules. Furthermore, conformational changes and assemblies of very large macromolecular complexes, which can be propagated through long distances (tens of angstroms), are the effect of local interactions between small molecules (like messengers) or macromolecules with their cellular targets. In conclusion, small molecules control an enormous amount of cellular functions by binding to their target macromolecules, firing complex cellular pathways characterized by reactions, environmental changes, intermolecular interactions, and allosteric modifications.

In short, a deep understanding of the molecular basis of ligand-target interactions requires the integration of biological complexes into cellular pathways, that is "systems biology". In the other hand, systems biology (see, e.g., [2,3]), needs to be accompanied by a quantitative molecular description of pathways, so far most lacking. This novel area of investigation will impact strongly on pharmaceutical sciences and toxicology, as drugs target (and mutations affect) pathways, rather than a single biomolecule. It is also crucial in areas such as nanobiotechnology and in bioprocessing techniques.

World-wide projects such as the structural genomics, that are pushing forward the entire field of structural biology, will be able in a near future to produce such important results that it will be difficult to find a single protein for which no structural information is available or for which structural information is not readily accessible by straightforward [4]. It is probable that a near-complete structural picture will be available for most of the proteins in any given organism soon. However, structural biology remains limited in terms of the outcomes that it can offer to the community and still find difficulties when dealing with big macromolecular complexes. Large protein complexes or whole systems still require years of study for a detailed structural understanding to be reached. Thus, computational biology complemented with X-ray crystallography and carefully designed molecular biology experiments may be the key to face these difficulties.

Results and Discussion

Known structures, predicted interactions and predicted binding sites can greatly illuminate the understanding of a pathway. Very recently [5] we have tried to give structural detail to different proteins and complexes present on the pathway fundamental for the degradation of polycyclic aromatic hydrocarbons (PAHs). PAHs are widespread in the environment and persist over long periods of time: many polycyclic aromatic hydrocarbons (PAHs) are largely suspected to be mutagenic or carcinogenic [6] and their contamination in soil and aquifer is of great environmental concern. Among the PAHs, dibenzothiophene (DBT) represents the prevailing compound, and is generally considered as a model chemical structure in studies dealing with either biodegradation of organo-sulfur contaminants by petroleum biodesulfurisation through the "4-S pathway" [7] or through the "Kodama pathway" [8-10] Figure 1. When degraded through the latter pathway, the molecule is transformed into 3-hydroxy-2-formylbenzothiophene (HFBT). Di Gregorio and collaborators, very recently have identified a novel genotype for the initial steps of the oxidative degradation of dibenzothiophene, found in the bacterial strain *Burkholderia fungorum* DBT [11].

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Burkholderia fungorum DBT1 is a NON-PATHOGENIC strain capable of transforming DBT completely through the "Kodama pathway" with higher efficiency than other microorganisms. The first step of the Kodama pathway was shown to be catalyzed by the Rieske Oxygenase (RO) systems [12], forming *cis*-dihydrodiols from a large variety of substrates and molecular oxygen (dioxygen).

Detail of the initial step: RO systems (in the box, composed by reductase, ferredoxin and an oxigenease) use electrons from NAD (P) H to activate molecular oxygen, which is then used to oxidize the substrate. The reductase component liberates electrons from NAD (P) H and transfers the electrons to the ferredoxin, that shuttles the electrons to the oxygenase, where they are used in catalysis. This component consists of an alpha subunit, which contains both a Rieske binding domain and a catalytic domain. A beta subunit is present, which is believed to primarily function as a stabilizer for the alpha subunits. Rieske Oxygenase (RO) systems of *Burkholderia fungorum* DBT1 is called dibenzothiophene dioxygenase [11]. Homology models were produced for each of the proteins shown. This structural information covers only a small fraction of the possible interactions between these families of ligands and receptors.

While structural studies have been performed on a number of ROs, no crystal structure exists for the DBT1 enzymes. Dibenzothiophene dioxygenase is able to degrade a wide spectra of molecules, including naphthalene, phenanthrene and DBT [13]. For its particular characteristics, Burkholderia fungorum DBT1 might be interestingly exploited in bioremediation protocols of PHA-contaminated sites. Our initial studies comprised the structural modeling of all the players of the initial step in the Kodama pathway for the degradation of PAHs by the *Burkholderia fungorum* DBT1 strain. The availability of several structural evolutionary correlated templates, covering the entire RO complex gave us the possibility of building not only the structural models of the isolated components but also to gain insight into the big protein complexes involved in the process. The possibility of modeling one of the most important proteins complexes and its validation with experiments extracted from literature, prompted us to hypothesize that more refined models will offer more a important overview of the system under study and may allow the full characterization of the entire pathway Figure1.

Combining pathways with 3D details ultimately makes them more useful for the complete characterization of bio-systems. Indeed, if the nature of an interaction is known, then it may be easier to estimate the affinity of the association. Crystal structures or models can give clues about the interaction regions, indeed, they can also give insights into the order of interaction events in a pathway, by indicating which interactions cannot occur simultaneously or which of them may compete for a similar binding region. It may also provide elements for an intelligent design of inhibitors, providing a rational basis for deciding how to interfere with a pathway.

The previous example illustrates how known structures, when combined with modeling, can provide insights into the interacting components of a well-studied pathway. However, a more interesting possibility is to use interaction modeling/prediction as a means to propose new pathway elements, or indeed pathways that are completely new. Joining this information with methods for prediction of protein interactions can be used to give insights into the molecular details of the interactions, and therefore to give some guidance regarding the order of events (see above). Such approaches might also allow us to determine whether clusters of interacting proteins correspond to a single large complex or to a set of proteins that belong to a pathway.

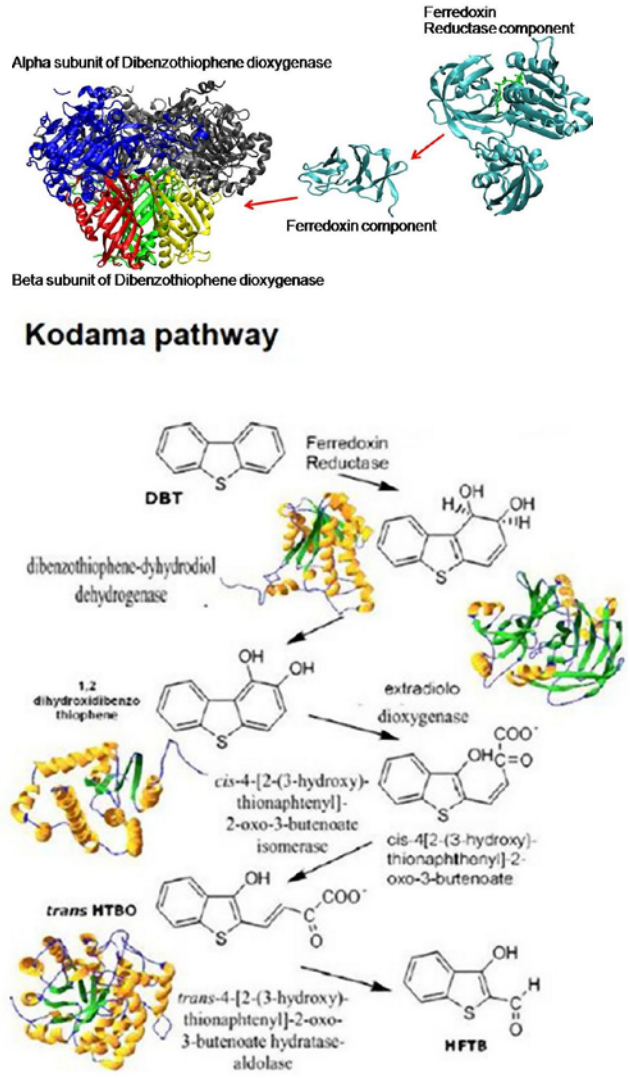

Figure 1: Kodama pathway.

A last word

Proteomes and interactomes, albeit extremely useful for the characterization at a macro level of the functioning of a whole cell, provide a rather abstract network of macromolecules. However, the distance to a real physical picture is very large. Indeed, a more concrete description of the cell networks will arrive when complete interaction pathways will be complemented with all-atom three dimensional structures of protein complexes. This kind of information will confer an extremely important novel role to experimental/computational structural biology in the field of systems biology. Indeed, structural information for interacting cellular components will produce a more and more complete all-atom-detail scaffold for the characterization of entire cellular pathways, which will be of immense benefit to anybody studying or modeling biological systems.

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