System Biology Approaches to Identify Biomarker in Liver Diseases

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Abstract

System biology emerging from year 2000 onwards in biomedical sciences is multi disciplinary approaches focus on complex dynamics interaction with in biological system. Alcohol and other drugs are potent cause of liver failure in USA and Worldwide. We describe system biology approaches a potential tool for identifying cell signaling pathways and co expressed genes involved in liver toxicity induced by reactive oxygen species, free fatty acids, and TNFα in liver hepatocyte, kupffer cell and stellate cells. System biology approaches analyzed multiple omics data i.e. Phenomics, Genomics, Epigenomics, Lipidomics, Metabolomics, Transcriptomics and Proteomics etc. to understand gene expression, metabolic profile, toxicity profile to predict and validate or characterized gene targets for liver toxicity.

1. Introduction

One of the most important aims of systems biology is to model and discover emergent properties of cells, tissues and organs functioning as a system whose theoretical description is only possible using techniques which fall under the remit of systems biology. These typically involve genome wide metabolic networks or cell signaling networks (Bu and Callaway 2011). Integrated system biology is an inter disciplinary field of study that focus on inter disciplinary study focus on complex interaction within biological system. System Biology is defined from a number of different aspects is as follows (Wikipedia.org).

2. Field of Study

study interaction between components of biological systems and how these interactions give rise to function and behavior in that system. e.g. enzymes and toxicant in a metabolic pathway.

3. Paradigm

usually defined antithesis to the so call reductionist paradigm (biological organization), although fully consistent with the scientific method. Systems biology explains putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programs, but different, It means changing our philosophy, in the full sense of the term" (Denis Noble, 2006).

4. Operational Protocols Used for Performing Research

It consist of theory, analytic or computational modeling to propose specific hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of cells or cell processes to refine the computational model or theory (Kholodenko et al., 2005). The objective is a model of the interactions in a system, the experimental techniques that most suit systems biology are those that are system-wide and attempt to be as complete as possible. Therefore genomics, transcriptomics, metabolomics, proteomics, epigenomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models.

5. Dynamic System Theory to Molecular Biology

This focus on the dynamics of the studied systems is the main conceptual difference between systems biology and bioinformatics.

6. Socio-scientific Phenomenon

It is defined as the strategy of pursuing integration of complex data about the interactions in biological systems from diverse experimental sources using interdisciplinary tools and personnel.

Integrated system biology is the interdisciplinary study of systems in general including different omics approaches with the goal of elucidating principles that can be applied to all types of systems at all nesting levels in the field of research. Systems biology established its ancestry in the quantitative modeling of enzyme kinetics, a discipline that flourished between 1900 and 1970, the mathematical modeling of population growth, the simulations developed to study neurophysiology, and control theory and cybernetics. Karl Ludwig von Bertalanffy was an Austrian-born biologist known as one of the founders of general systems theory (GST).

The first numerical simulations in system biology was published in 1952 by the British neurophysiologists and Nobel prize winners Alan Lloyd Hodgkin and Andrew Fielding Huxley, who developed a mathematical model that explained the action potential propagating along the axon of a neuronal cell (Hodgkin and Huxley, 1952). The model described a cellular function emerging from the interaction between two different molecular components, a potassium and a sodium channel, and can therefore be seen as the beginning of the computational systems biology (Le Novere, 2007). In 1960, Denis Noble developed the first computer model of the heart pacemaker (Noble, 1960). The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology"(Mesarovic, 1968; Rosen 1968). During 1960s and 1970s occurred the development of several approaches to study complex molecular systems, such as the Metabolic Control Analysis and the biochemical systems theory. The successes of molecular biology throughout the 1980s, coupled with a skepticism toward theoretical biology, that then promised more than it achieved, caused the quantitative modeling of biological processes to become a somewhat minor field. However the birth of functional genomics in the 1990s meant that large quantities of high quality data became available, while the computing power exploded, making more realistic models possible. Around the year 2000, after Institutes of Systems Biology were established in Seattle and Tokyo, systems biology emerged as a movement in its own right, spurred on by the completion of various genome projects, the large increase in data from the omics (e.g. genomics and proteomics) and the accompanying advances in high-throughput experiments and bioinformatics. Since then, various research institutes dedicated to systems biology have been developed (Wikipedia.org).

7. System Biology Approaches for Liver Toxicity Pathways

Li and Chan., 2009 describe approaches identifying pathways involved in liver toxicity induced by free fatty acids (FFA) and tumor necrosis factor (TNF)-α in human hepatoblastoma cells ($HepG_2/C_3A$). Systems biology methodologies were developed to integrate multi-level data, i.e., gene expression, metabolite profile, toxicity measurements and a priori knowledge to identify gene targets for modulating liver toxicity. Gene Module map analysis [Segal et al., 2004] was applied to identify the important pathways perturbed by FFA treatment using Genomica (available at [http://genie.weizmann.ac.il]). 350 biologically meaningful gene sets were first defined based upon their functional category or pathways defined in the MsigDB database [Subramanian et al., 2005]. Three-Stage-Integrative-Pathway-Search (TIPS) framework TIPS approach was developed to integrate gene expression and toxicity measurement to identify toxicity relevant gene targets and pathways. Three methods, including genetic algorithm coupled partial least squares analysis (GA/PLS), constrained independent component analysis (CICA) and Bayesian network analysis (BN) were integrated within the framework (Srivastava et al., 2007). The analyses identified NADH dehydrogenase and mitogen activated protein kinases (MAPKs) were relevant to both cytotoxicity and lipid accumulation. Indeed, inhibiting NADH dehydrogenase and c-Jun N-terminal kinase (JNK) reduced cytotoxicity significantly and increased intracellular TG accumulation. In fact much greater reduction in the toxicity was observed upon inhibiting the NADH dehydrogenase or MAPK than for the stearoyl-CoA desaturase (SCD) activation [Srivastava et al., 2007]. Analysis found ketone bodies, such as acetoacetate and beta-hydroxybutarate, were found to be highly relevant to the toxic phenotype. Second, we identified toxicity relevant gene sets with gene set enrichment analysis (GSEA) analysis. Li and Chan., 2009 found gene sets, such as ROS, ETC, PPP and fatty acid metabolism were significantly enriched. Finally, multi-block partial least squares (MBPLS) was applied to identify individual genes that were relevant to the aforementioned metabolites and in turn toxicity. Genes, such as glutathione S-transferase, NADH dehydrogenase and ALDH1A1, were identified to be relevant based upon their regression coefficients.

8. Protein Interaction Network of Liver

Wang et al., 2011 map the interactions of an unbiased selection of 5026 human liver expression proteins by yeast two-hybrid technology and establish a human liver protein interaction network (HLPN) composed of 3484 interactions among

2582 proteins. SPOP, TNIP1, TRAF1, IKBKG, TNFAIP3 and NFKBIB were identified as putative binding partners of the GPCR-kinase interacting protein 2 (GIT2). Of these partners, TNFAIP3 (tumor necrosis factor, a-induced protein 3) and TNIP1 are subunits of the TNFAIP3 ubiquitin-editing complex, which mediates the deubiquitination of IKBKG and negatively regulates the NF-kB pathway (Wertz et al, 2004; Oshima et al, 2009). GIT2 is a ubiquitous multi domain protein that has an important role in the scaffolding of signaling cascades (Hoefen and Berk, 2006). Therefore, we proposed that GIT2 may be involved in the NF-kB pathway through regulation of the interaction between IKBKG and TNFAIP3. To test this hypothesis, we confirmed the interaction between GIT2 and IKBKG. The over expression of GIT2 enhanced the deubiquitination activity of TNFAIP3 toward IKBKG, and siRNA targeted at GIT2 abrogated the TNFAIP3-dependent deubiquitination of IKBKG and impaired the ability of TNFAIP3 to inhibit NF-kB activation. This finding suggests that endogenous GIT2 plays a role in negatively regulating inducible NF-kB activity. In the HLPN, 279 proteins were distributed among 11 signal transduction pathways in the KEGG; these proteins were mainly involved in MAPK, ERbB, VEGF, Wnt, TGF-b and other signaling pathways that participate in the regulation of liver functions (Wang et al., 2011).

9. A Systems Biology Approach to the Pathogenesis of Obesity-related Nonalcoholic Fatty Liver Disease (NAFLD)

A comprehensive analysis of 54 different kinase substrates and cell signaling endpoints showed that an insulin signaling pathway is deranged in different locations in NAFLD patients. Furthermore, components of insulin receptor–mediated signaling differentiate most of the conditions on the NAFLD spectrum. For example, PKA (protein kinase A) and AKT/mTOR (protein kinase B/mammalian target of rapamycin) pathway derangement accurately discriminates patients with NASH from those with the non-progressive forms of NAFLD. PKC (protein kinase C) delta, AKT, and SHC phosphorylation changes occur in patients with simple steatosis. Furthermore, amounts of cleaved caspase 9 and pp90RSK S380 were positively correlated in patients with NASH. Amounts of the FKHR (forkhead factor Foxo1) phosphorylated at S256 residue were significantly correlated with AST/ALT ratio in all morbidly obese patients. Specific insulin pathway signaling events are altered in the adipose tissue of patients with NASH compared with patients with nonprogressive forms of NAFLD. These findings provide evidence for the role of omental fat in the pathogenesis, and potentially, the progression of NAFLD (Calvert et al., 2007). A substantial component of the signaling differences corresponded to other pathways such as eNOS and cAbl.

10. Serum MicroRNAs as Specific Biomarkers for Diagnosis of Liver Injury in Rats

In order to identify candidate miRNAs as diagnostic biomarkers for drug induced biomarker for liver injury, miRNA expression profiles of serum and liver tissue from two parallel liver injury Sprague-Dawley rat models induced by a compound (acetaminophen, APAP) or an herb (Dioscorea bulbifera, DB) were compared. Two sets of dysregulated miRNA candidates in serum and liver tissue were selected in the screening phase. In the dose-dependent analysis of the serum miRNAs miR-122, miR-192 and miR-193 showed extremely high sensitivity in both 2 model groups (fold change >50.0), while serum biochemical parameters (e.g., ALT and AST) displayed only mild sensitivity (fold change, <20.0) in the high-dose group. All 3 serum miRNAs demonstrated better sensitivity than serum biochemical parameters in the middle- and low-dose group, but serum miR-122 was much more sensitive than biochemical parameters (Su et al., 2012).

11. Conclusion

Integrated system biology is unique approach to study molecular biological change liver pathology. Genetics and genomics approaches study changes in gene expression during liver disease. System biology measures genome wide cell signaling network during perturbation or cellular stress. Recently it has been discovered the role of micro RNA, long non coding RNA has genome wide binding targets and regulate cell signaling networks in liver diseases.

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