SYSTEMS MOLECULAR NEUROSCIENCE: FOCUS ON POLYGLUTAMINE DISORDERS

NEUROCIENCIA MOLECULAR DE SISTEMAS: ÉNFASIS EN ENFERMEDADES POLIGLUTAMÍNICAS

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Abstract

Systems biology offers a valuable alternative to the classic “oslerian” approach to disease, particularly in the case of polyglutamine disorders. Efforts have been made to clarify the ´disease-home´ of polyglutamine disorders, particularly of Huntington´s disease and several Spinocerebellar Ataxias, through transcriptomic, proteomic and bio-informatics studies. The epistemic issue of ´causality´ raised by these functional studies can be solved by genome-scale loss of function studies, although the integration of the large amounts of heterogeneous information generated by these studies remains a challenge. It is expected that the application of system biology approaches to polyglutamine disorders will led to a personalized medicine at the patient level and to the discovery of effective therapeutics.

Key words: biological networks, polyglutamine disorders, proteomics, systems biology, transcriptomics

Resumen

La biología de sistemas ofrece una valiosa alternativa a la visión “osleriana” clásica de enfermedad, particularmente en el caso de las enfermedades poliglutamínicas. Se han realizado esfuerzos por esclarecer los vínculos entre módulos funcionales discretos en estas enfermedades, particularmente en la enfermedad de Huntington y varias Ataxias Espinocerebelosas, a través de estudios de transcriptómica, proteómica y bio-informática. El problema epistemológico de la ´causalidad´ ligado a estos estudios funcionales, puede ser resuelto a través de estudios de pérdida de función a escala genómica, aunque la integración de la gran cantidad y heterogeneidad de la información generada sigue siendo un asunto a superar. Se espera que la aplicación del enfoque de biología de sistemas a las enfermedades poliglutamínicas conduzca a una medicina personalizada a nivel del paciente y al descubrimiento de tratamientos efectivos.

Palabras clave: redes biológicas, enfermedades poliglutamínicas, proteómica, biología de sistemas, transcriptómica

Introduction

Systems biology is an evolving field in the landscape of biological sciences to deal with the complexity of life. It is an attempt to supersede the classical reductionism view in biology to be replaced with an approach that involves high throughput data acquisition, accurate quantization and mathematical modeling (1). Although a full definition for systems biology is hard to get, as frequently happens with significant ideas, specialists coincide this is about the integration of large amounts of data into a unifying conceptual framework characterized for being inter-disciplinary, comprehensive, iterative, dynamic, quantitative and with predictive power (2). As Richard Feynman quoted “it is not always a good idea to be too precise” (3), as seems to be the case for systems biology.

It is expected that the generation of predictive mathematical models of biological systems will be useful for finding out sub-cellular mechanisms of metabolism regulation or to more effective drugs discovering avoiding the usual need for testing them on patients in the first phases of their validation (4). Systems biology is then a novel approach that targets essential properties of complex biological systems, that is: emergence, robustness and modularity (2).

The systems biology approach has been applied to a number of disciplines, then sprouting sub disciplines such as “systems neuroscience”, which is devoted to the study of the function of neural circuits and systems. “Systems neuroscience” is an umbrella term, encompassing diverse fields of study concerned with the link between molecular and cellular approaches to understanding brain structure and function (5). Significant progress has been made in the comprehension of high-level brain functions such as language, memory, and consciousness, as well as the molecular and neural mechanisms involved in life-threaten disorders like Alzheimer’s and Parkinson’s diseases and polyglutamine disorders such as Huntington’s diseases and several spinocerebellar ataxias (6-9). It is expected that this in deep understanding resulting from the application of the novel framework of systems biology, will lead to improved therapeutics for the treatment of patients suffering from such a pervasive disorders.

This review is intended to provide and updated and critical picture of the potentiality of the systems biology approach in the field of molecular neuroscience with emphasis on polyglutamine disorders.

On the precursors of modern systems biology

Although the fundamentals of complexity thinking in biology came to light more than a hundred years ago, the modern conceptions arose with the technological improvements promoted by the Human Genome Project, the first international mega-project in the history of biological sciences. The development of high throughput DNA sequence analyzers, DNA micro-arrays and mass spectrometry, as well as computational and bioinformatics’ algorithms and software are in the base of systems biology for permitting the acquisition and processing of large volumes of data (1).

Going backward into the theoretical foundations of systems biology it is usual a reference to Emmanuel Kant philosophical notions on living organisms as resulting from the inter-connectedness of its basic constituents: “organisms are organized natural

products in which every part is reciprocally both end and means". In 1941, Beadle and Tatum published their crucial paper on the hypothesis ''one-gene/one-enzyme/one-function" where they stated that ''since the components of such system are likely to be interrelated in complex ways, it would appear that there must exist orders of directness of gene control ranging from simple one-to-one relations to relations of great complexity" (10). Later in 1949 there was the attempt of Delbrück to explain the phenomenon of differentiation (11) and in 1957 was published the paper ''Enzyme induction as an all-or-none phenomenon" by Novick and Weiner, where was concluded that an extremely rapid induction of lacZ-encoded b-galactosidase (b-Gal) triggered by a lactose analog is obtained if one observes the response at the cellular level rather than for an entire cell population (12). Also in 1957 Waddington proposed the notion of `epigenetic landscape` referring to the ''route" that a complex biological system might be crossing in response to genetic, developmental or environmental cues (13). Four years later, in 1961, Monod and Jacob refer to the probable involvement of positive feedback circuits for bistability, and negative feedback circuits for homeostasis and oscillatory phenomena (14). In 1966 was launched the formal study of systems biology by systems theorist Mihajlo Mesarovic (15), and three years later Kauffman proposed the theoretical modeling of ''randomly constructed genetic nets" (16). In 1968, Ludwig von Bertalanffy with his *General Systems Theory* had proposed to look at biological system as a unity operating in its internal dynamics -explained by the relations between its components and the regularities of their interactions- but also to see it in its circumstances (17).
All those above mentioned studies contributed greatly to the sprouting of modern systems biology. However, another significant precursor is usually skipped away in the literature. We refer to the work of A.L Hodgkin and A.F Huxley on electrical currents on excitable tissue (18). The Hodgkin-Huxley model on electrical currents on excitable tissue is usually considered as one of the great achievements of 20th-century biophysics, as well as one at the root of systems biology.

Rephrasing the Oslerian approach to disease

William Osler (1849-1919) has been properly named as one of the greatest icons in modern medicine. His characterization and definition of human disease based on a clinicopathological correlation that links clinical presentation with pathological findings, has held sway for over a century, since its proposal back in 19th century until today. This paradigm has been quite useful to clinicians as it establishes syndromic patterns that constrain the number of possible clinical phenotypes they may need to ponder. However, this approach excessively generalize clinical phenotypes, does not take into consideration preclinical disease stages and it is useless to tailor diagnosis or therapy (19). In the current context of systems biology, a rephrase of disease definition is needed.
From a system´s biology point of view all disease is complex, even the so called "simple" Mendelian disorders. This complexity is soaked up in the fluid conception of clinical phenotypes as a result of "defective molecular network within a stochastic environmental context that modulates network function" (19, 20). Actually, only about 10% of human genes are known to be associated with a disease (21), remarking the idea of molecular networks instead of isolated genes, RNAs or proteins as disease causative agents.

Disease modules and networks. The ´disease-ome´

As mentioned before, modularity is conceived as one of the essential properties of complex biological systems. Broadly speaking, this concept reflects that a group of items work together and they are less coupled to items within other groups. From a molecular biological point of view, a module is made up of genes/RNAs/proteins acting coordinately to accomplish a function that is semiautonomous from other functions (22).
It has been proposed that disease-related components of a network are likely to comprise a “disease module”. This notion is supported by the fact that there is 10-fold increase in the number of physical interactions observed between gene products associated with the same disorder than would be expected by chance (23). Additionally, genes linked to diseases with similar clinical phenotypes have an increased probability of interacting with each other than those not linked to the clinical phenotype (24, 25). Considering these observations, a “disease module” can be defined as a sub network -or group of network components- in the global molecular network that mirrors a distinctive set of distant or neighboring interactions that contribute to an abnormal phenotype when one or more of its constituents are dysfunctional (19). Disease modules can overlap as one or several specific components -genes, RNAs or proteins- of a particular module can participate in more than one disease modules (26).
Disease modules can be identified either by means of bioinformatics or experimental approaches; this search relies on two assumptions: 1) disease modules are often related with common, highly interconnected local groups of nodes that can be identified by network clustering algorithms; and 2) the nodes of a disease module relate to cellular components of similar or closely linked functions associated within a specific area of the network (27).
Systematic mapping of disease modules have progressively led to the idea that they are usually interdependent and to the derived construction of a higher level network of disease nodes linked together by their common molecular foundations, or disease-ome. There are at least three different representations of the disease-ome: the shared gene formalism, the shared metabolic pathway formalism, and the disease co-morbidity formalism (19). The first one recognizes that probably diseases have a common genetic basis if they share one or several genes. The second representation states that enzymatic defects that disturb the occurrence of a chemical reaction in an specific metabolic pathway may disrupt downstream reactions in the same pathway leading to clinical phenotypes that are recognized to be connected with the downstream reactions (28). Finally, the third representation establish connections among diseases based on their co-occurrence in a frequency larger than expected by chance; this view leads to the elaboration of phenotypic disease network maps (29) (Figure 1).
These system biology approaches have been used to identify disease modules for an increasing number of neurological diseases including polyglutamine disorders (6). But, how these new approaches have impacted on basic knowledge and therapeutics for these diseases?

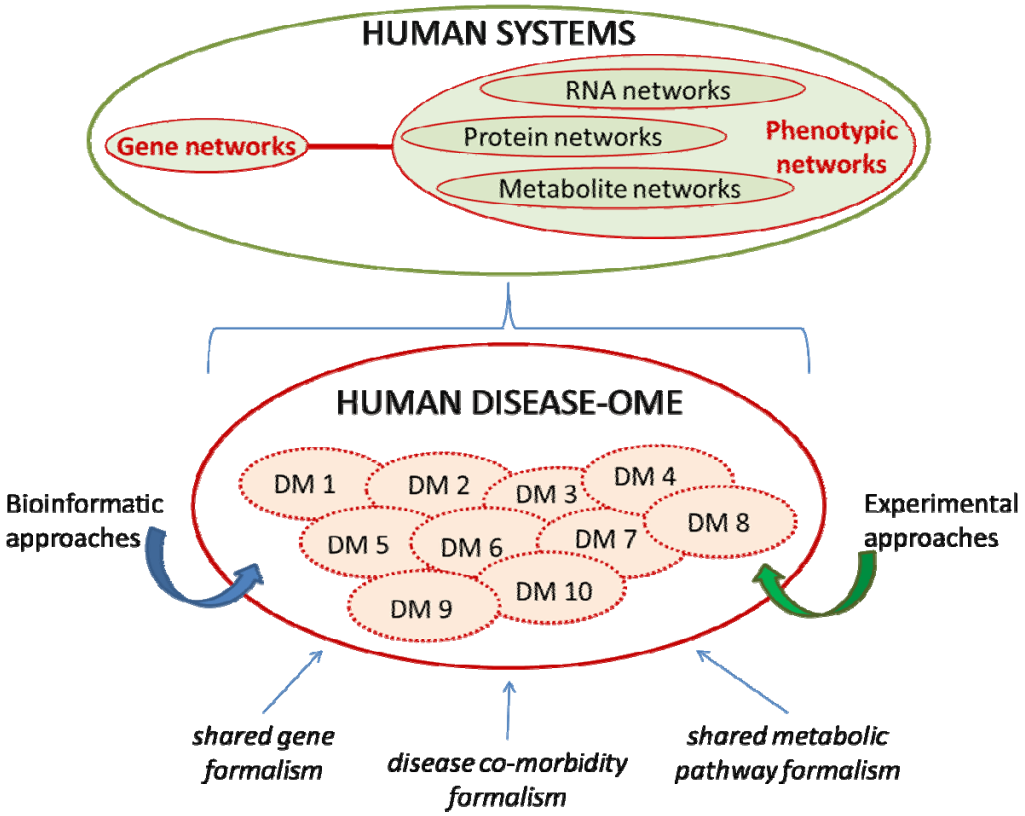

Fig.1. The human systems biology world. DM- Disease module. (Modified from: Loscalzo y Barabási, 2011).

Systems biology in the study of polyglutamine disorders

Polyglutamine (polyQ) disorders are a group of inherited neurodegenerative conditions that so far include Huntington's disease, dentatorubralpallidoluysian atrophy, spinal bulbar muscular atrophy, and six of the spinocerebellar ataxias (SCAs) -1, 2, 3, 6, 7 and 17. In each case, different ubiquitously expressed genes harbor expanded CAG repeat mutations which are translated into proteins with expanded polyQ tracts that eventually lead to the dysfunction and degeneration of specific neuronal subpopulations. Proposed pathogenic mechanisms for polyQ disorders include impaired ubiquitin proteasome pathway (UPS), transcriptional dysregulation, excitotoxicity, oxidative stress and mitochondrial dysfunction (30). Recent functional studies at transcriptomic and proteomic levels performed in animal models and humans have made possible to get a deeper knowledge on the molecular mechanisms involved.

Huntington´s disease

Huntington disease (HD) is a progressive neurodegenerative disorder with an established autosomal dominant inheritance pattern and symptoms that are referable to specific regions of brain disease. It is associated with a wide variety of movement, cognitive and psychiatric disorders caused by an expanded CAG repeat in the HTT gene, which codes for a protein called huntingtin (*htt*). The worldwide prevalence of HD

has been estimated to be approximately 2.7 per 100,000, but there is wide variation in worldwide prevalence rates (31).

Transcriptional deregulation is one of the pathogenic mechanisms proposed for polyglutamine disorders and for HD in particular (32). By using high-throughput real-time PCR (RT-PCR) in inducible PC12 cell lines expressing an amino-terminal fragment of the *htt* protein, it were found 126 differentially expressed genes, about one-quarter of which were down-regulated by the expression of human *htt*. Five of these down-regulated genes [Glut1 (glucose transporter 1), Pfkm (phosphofructokinase muscle isozyme), Gstm2 (prostate glutathione-S-transferase 2), Rbm3 (RNA-binding motif protein 3) and Krip-1 (KRAB-A interacting protein 1)], when expressed in transiently transfected cell, significantly suppressed cell death in both neuronal precursor and non-neuronal cell lines, suggesting that these transcriptional changes were relevant to polyglutamine pathology (33). On the other hand, microarray studies revealed a large number of genes being down- or up-regulated in cell and transgenic mouse models, as well as in humans. The results of these studies vary depending on the methodology they used. For instance, several studies being performed in the R6/2 transgenic mouse striatum have revealed either more down-regulated than up-regulated genes (34) or the opposite (35). In humans it has been found more genes increased than decreased, with most prominent changes in striatum and motor cortex (36, 37).

Several studies have been performed at the protein level by using mass spectrometry approaches for the identification and quantitation of specific differentially expressed proteins in HD (38, 39). These studies have identified proteins functionally linked to key cellular processes like stress response, protein folding and degradation by the proteasome complex, and energy metabolism. In addition, the high-throughput Yeast Two Hybrid approach has been applied to the identification of *htt* interacting partners (40, 41). Some of the validated *htt* interacting proteins were identified as modifiers of the neurodegenerative process triggered by mutant *htt* in a fly model (40), and constitute better therapeutic targets than *htt* itself.

In addition to experimental approaches, there are several valuable databases and algorithms like Gene Multiple Association Network Integration Algorithm (GeneMANIA) (42) and Search Tool for the Retrieval of Interacting Genes (STRING) (43) allowing searching for interacting partners, building protein-protein interaction networks of variable density, and proposing hypothesis to be tested by functional studies (Figure 2). There are also databases like Protein Analysis THrough Evolutionary Relationships (Panther) (44) that contain pathological pathways involved in HD. These databases integrate curated information coming from functional studies and data mining. However, one major problem to integrate transcriptomic, proteomic and additional “omic” data into a comprehensive pathologic model remains on the fact that it is not clear if these transcription or protein changes are causative or epiphenomenal.

Experimental studies have been devised to overcome the problem of causality in transcriptomics and proteomics studies. Approaches like large-scale RNAi screens belong to a more general class of genome-scale loss of function studies and provides a valuable cause-to-effect platform (45). The results of RNAi screens have led to new understandings of gene functions and networks in the context of HD. Several genetic modifiers of *htt* toxicity and aggregation have been identified, mainly linked to RNA synthesis and processing and to proteins folding, transport and degradation in *Caenorhabditis elegans* (46) and *Drosophila* models (47, 48). In addition to large-scale

RNAi screens, the genome-wide screens for chemically induced mutants approach has been applied to HD (49). By using this approach, MOAG-4/SERF was identified as a new modifier of mutant *htt* aggregation; this modifier was involved in a previously unexplored pathway, and it was showed that the mechanism has been conserved from worms to humans.

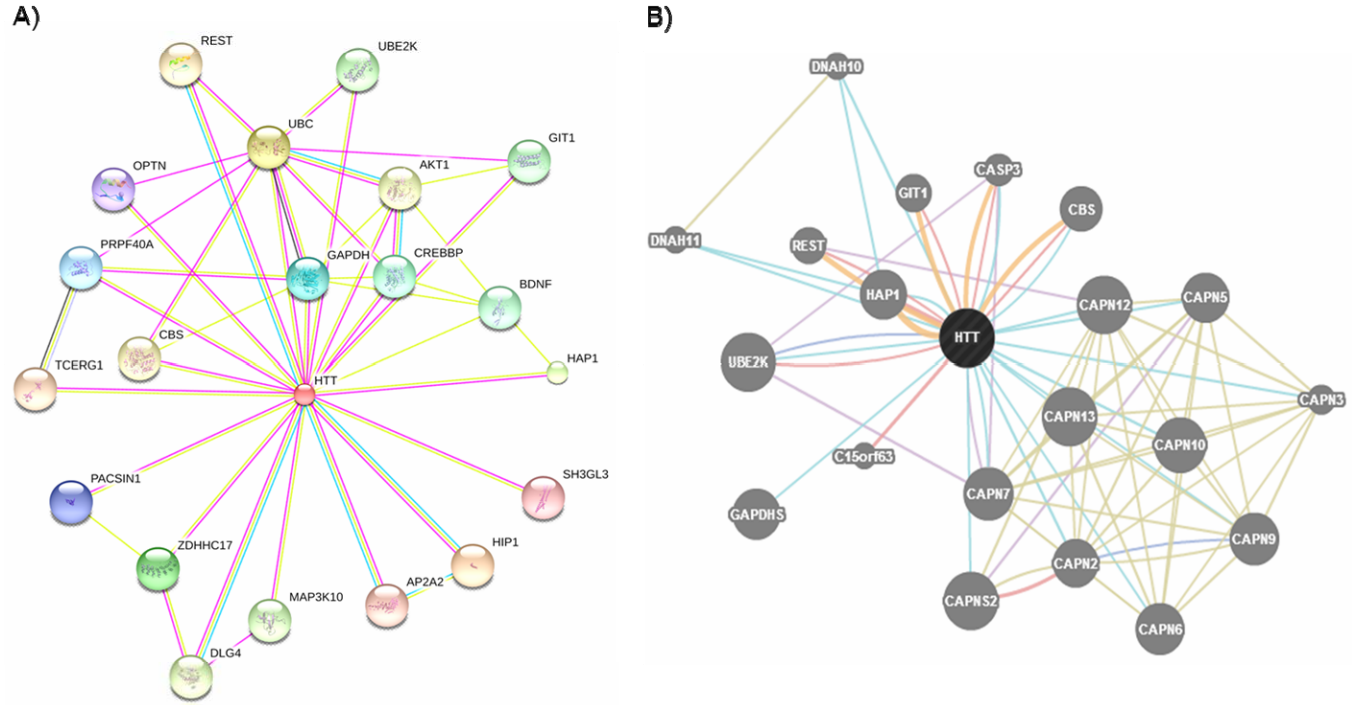

Fig. 2. Protein-protein interaction networks for *htt* protein in humans. A) The interacting proteins were retrieved from STRING database. B) The interacting proteins were retrieved from GeneMANIA database.

Spinocerebellar ataxias caused by CAG repeat expansions

Spinocerebellar ataxias (SCAs) encompass a clinically and genetically heterogeneous group of inherited neurodegenerative disorders mainly affecting the cerebellum, although further parts of the nervous system as well as extra-neural tissues can also be affected. At least seven of the SCAs –including dentatorubral pallidoluysian atrophy (DRPLA)- are caused by CAG repeat expansion mutations located in coding regions of their respective genes that are translated into polyglutamine tracts (50). Worldwide prevalence for SCAs have been estimated to be 5-7/100 000 inhabitants (51).

Relative to HD, little have been done to clarify the disease-ome for the SCAs caused by CAG repeat expansion mutations. A protein-protein interaction network for human inherited ataxias was generated by using Yeast Two-Hybrid screens; results were validated by co-affinity purification experiments and bio-informatics analysis (52). By these means, 770 mostly novel protein-protein interactions were identified. It was shown that many ataxia-causing proteins share interacting partners, actually 18/23 of the ataxia-causing proteins interact either directly or indirectly; a subset of these interactions have been found to modify neurodegeneration in animal models. According to Gene Ontology analysis, most of the members of the ataxia network are transcription regulators located in the nucleoplasm and mainly acting as transcriptional co-repressors

(52). This “ataxia-ome” provides a mean for an in-deep understanding of the molecular basis of human hereditary ataxias and for prospective identification of new candidate genes for inherited ataxias (53).
Computational prediction of biological networks has been also applied to Spinocerebellar ataxias (54). Using a moving window bio-informatic approach, a screen was made to identify transcripts with partial identity to the 5´ and 3´ untranslated regions of the polyQ SCA genes ATXN1, ATXN2, ATXN3, CACNA1, ATXN7 and TBP. Several transcripts were identified as interactors of proteins directly involved in SCAs; most of them belong to transcription control and RNA binding functional groups. The most significant pathways identified by using this approach were the insulin growth factor pathway, the WNT pathway, long term potentiation, melanogenesis and ATM mediated DNA repair pathways. Some proteins were identified as being statistically significant in the polyQ proteins network, this include PAXIP1, CELF2, CREBBP, EBF1, PLEKHG4, SRSF4, C5orf42, NFIA, STK24, and YWHAG proteins. All these proteins should be explored as potential biomarkers or possible therapeutic targets (54).

Conclusions

Systems biology offers a valuable alternative to the classic “oslerian” approach to disease, particularly in the case of polyglutamine disorders. The issue of causality raised by transcriptomic and proteomic analysis can be solved by genome-scale loss of function studies, although the integration of the large amounts of heterogeneous information generated by these studies remains a challenge in order to understand polyglutamine disorders at the patient level and to devise promissory therapeutics.

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