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Special Article

Systems medicine: A new approach to clinical practice☆

Pablo Cardinal-Fernández,[a,b] Nicolás Nin,[b,c] Jesús Ruíz-Cabello,[b,d,e] José A. Lorente[a,b,f,*]

[a] Servicio de Medicina Intensiva, Hospital Universitario de Getafe, Madrid, Spain
[b] CIBER de Enfermedades Respiratorias, Madrid, Spain
[c] Servicio de Medicina Intensiva, Hospital Universitario de Torrejón, Madrid, Spain
[d] Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain
[e] Universidad Complutense de Madrid, Madrid, Spain
[f] Universidad Europea de Madrid, Madrid, Spain

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ABSTRACT

Most respiratory diseases are considered complex diseases as their susceptibility and outcomes are determined by the interaction between host-dependent factors (genetic factors, comorbidities, etc.) and environmental factors (exposure to microorganisms or allergens, treatments received, etc.).

The reductionist approach in the study of diseases has been of fundamental importance for the understanding of the different components of a system. Systems biology or systems medicine is a complementary approach aimed at analyzing the interactions between the different components within one organizational level (genome, transcriptome, proteome), and then between the different levels.

Systems medicine is currently used for the interpretation and understanding of the pathogenesis and pathophysiology of different diseases, biomarker discovery, design of innovative therapeutic targets, and the drawing up of computational models for different biological processes.

In this review we discuss the most relevant concepts of the theory underlying systems medicine, as well as its applications in the various biological processes in humans.

Medicina de sistemas: una nueva visión de la práctica clínica

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RESUMEN

La gran mayoría de las enfermedades respiratorias son consideradas patologías complejas puesto que su susceptibilidad o desenlace están influidos por la interacción entre factores dependientes del huésped (genéticos, comorbilidad, edad, etc.) y del ambiente (exposición a microorganismos y alérgenos, tratamiento administrado, etc.).

El enfoque reduccionista ha sido muy importante para la comprensión de los diversos componentes de un sistema. La biología o medicina de sistemas es una aproximación complementaria cuyo objetivo es el análisis de las interacciones entre los componentes dentro de un nivel de organización (genoma, transcriptoma, proteoma) y posteriormente entre los distintos niveles.

Las actuales aplicaciones de la medicina de sistemas incluyen la interpretación de la patogénesis y fisiopatología de las enfermedades, el descubrimiento de biomarcadores, el diseño de nuevas estrategias terapéuticas y la elaboración de modelos computacionales para los distintos procesos biológicos.

En la presente revisión se exponen las principales nociones sobre la teoría que subyace a la medicina de sistemas así como sus aplicaciones en algunos procesos biológicos del ser humano.

Introduction

Most respiratory diseases are considered complex, as their susceptibility and outcomes are determined by the interaction between host-dependent (genetic factors, comorbidities, etc.) and environmental factors (exposure to microorganisms and allergens, treatments received, etc.).

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* Corresponding author.
E-mail address: joseangel.lorente@salud.madrid.org (J.A. Lorente).

Table 1
Comparison between the reductionist and holistic approaches.

Example	Holistic approach Systems biology	Reductionist or mechanistic approach Molecular biology
Object of study	Interactions between all the elements of a system	Each element individually or in small groups
Complexity of the approach	High	Low (seeks to simplify as much as possible to draw conclusions)
Relationship between organizational levels	Complex, non-linear Laws or rules cannot be inferred from lower to upper organizational levels	Relatively simple and linear Based on ontogeny and epistemology
Visualization	By networks or graphs	Description of the characteristics of each element
External influence on the object of study	Major, especially environmental	The smallest possible

The advent of new, sophisticated techniques in the early 20th century enabled the function, structure and details of the *parts* of each biological system or process to be determined. It was the peak of the *reductionist* or *mechanistic* approach.

At the beginning of this century, newly motivated by technological developments capable of producing mass experimental and *in silica* data quickly and at a relatively low cost, the scientific paradigm shifted from the study of the *parts* to the study of the *interactions* that exist within a system. A specific disease can be considered a system.

Systems biology, therefore, can be defined as the field of study concerned with the analysis of complex interactions within a system with different scales of biological organization, from molecules to cells, organs, individuals, societies and ecosystems. *Systems biology* is characterized by the search for a quantitative description of biological processes, which includes multiple levels (genome, transcriptome, proteome, metabolome, etc.) and different time scales, based on data usually generated using high throughput technology, mathematical algorithms and computational models.[1] When the concept of *systems biology* is applied to the field of health sciences, it is called *systems medicine*. Systems biology and systems medicine are practically identical concepts, except that the former is general and the latter is particularly focused on medicine. Another unique feature of *systems medicine* is the frequent use of graphs, which have specific rules (analyzed in this article) while constituting a simple way of understanding and visualizing the results.

The field of *systems medicine* is currently undergoing tremendous development and has clear clinical implications. Some of its applications include the development of physiological and pathophysiological models, discovery of new drugs, and the development of diagnostic tests and novel biomarkers (Table 1).

This review is aimed at clinicians and is intended to convey the basics of *systems medicine* and some of its applications as simple as possible.

Systems medicine

The traditional reductionist approach centers on the analysis of specific molecules or processes from an individual's point of view, based on 2 types of concepts:

(a) *Ontological concepts*: all things are constituted by a limited set of primitive and indivisible material elements. Understanding the interaction between these basic compounds is sufficient to explain all complex phenomena.
(b) *Epistemological concepts*: the laws and theories in a given area and level of organization can be derived from lower (more fundamental) organizational levels.[2]

"Classical" molecular biology almost exclusively uses the reductionist approach, since it is based mainly on the characterization of molecules or genes and on explaining biological processes by combinations of interactions and properties among its components.

However, the study of the genome, cell metabolism and protein–protein interactions can be approached using global techniques and interpretations (holistic approach), based on the identification and analysis of the interactions between the different elements (nodes) of a network. These interactions are complex and include multiple organizational levels (DNA, RNA, proteins and environment, for example); they are non-linear (there is no directly proportional, easily deduced relationship between one organizational level and another); and they are redundant, and have multiple feedback loops. In this holistic approach, the concepts of ontogeny and epistemology are not applicable, since an element cannot be assigned an exclusive function, and neither is it possible to deduce the rules or laws of one level based on another organizational level.

The application of systems biology to specific medical issues has given rise to *systems medicine*, which allows new associations to be established between biological functions and special human diseases or conditions. For example, severe sepsis is caused by an infectious injury (bacteria, viruses, parasites), at a certain time (in the community or during a stay in it), in a host with certain characteristics (comorbidities, nutritional status, immune status, carrier of certain genetic polymorphisms). The response generated (alterations in transcriptome or proteome) is clearly influenced by the previously described factors and the treatment received. The aim of systems medicine is to analyze all these factors in a holistic and comprehensive manner, prioritizing the link between the different organizational levels on the functioning of each specific element.

Graphs and biological networks

Graphs used to display biological processes are called *biological networks*, and are a simple, easily understood way of visualizing information. A graph is a set of objects called *vertices* or *nodes* connected by *links* or *edges*. Airline connections are perhaps the best-known graphs. The nodes are the elements of interest, for example, proteins, genes, metabolites or in the aforementioned example, airports, while the *links* are the relationships between the nodes, and would correspond to flight routes between two airports. A graph, therefore, is defined by a set of nodes V (for example, airports) and links E (for example, routes), remembering that each link has two nodes (the airplane has to leave from one airport and arrive at another). Each link can be assigned a weight, direction and type.

Graphs have 3 main aims in the field of medicine:

(a) *To represent knowledge* of, for example, metabolic routes, transduction signals or gene expression.
(b) To quantify and visualize the data produced by experiments and high-throughput techniques, for example, data generated using microarrays or mass spectroscopy.