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Complexity in Asthma: Inflammation and Scale-Free Networks *

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ABSTRACT

Our understanding of asthma has traditionally been based on linear deterministic relationships of the type stimulus-bronchial hyperresponsiveness-obstruction-symptoms. This notion however neglects the fact that nonlinear relationships may be present. To better define the disease, some authors therefore suggest that we should think in terms of complex systems with a scale-free topology. The idea of multiple inflammatory hits proposed by the group of Pavord is in its broadest sense a further contribution to this line of thought. According to this theory, the coexistence of additional inflammatory stimuli, which may or may not be localized to the lungs, are responsible for deteriorating lung function. The effects of these stimuli may be additive or act in synergy with the underlying inflammation of asthma itself. In addition to the practical implications, this hypothesis serves as a reminder that the body is made up of interconnected parts and that the pathogenesis of asthma includes distinct elements linked together. If this hypothesis proves valid, future approaches should start to look for the hubs in this network that constitutes asthma, and attempt to integrate information from genomics, proteomics, and metabolomics.

La complejidad en el asma: inflamación y redes libres de escala

Palabras clave:
Asma
Inflamación
Redes libres de escala

RESUMEN

Tradicionalmente la interpretación del asma se ha fundamentado en relaciones deterministas directas del tipo estímulo-inflamación-hiperrespuesta bronquial-obstrucción-síntomas, olvidando, sin embargo, que en esta enfermedad no es infrecuente detectar circunstancias que no guardan linealidad. Por tal motivo algunos autores postulan que el abordaje de su patogenia debería comenzar a realizarse desde la óptica de los sistemas complejos que adoptan una topología libre de escala. La teoría de los impactos inflamatorios múltiples, propuesta por el grupo de Pavord, representa, en su sentido más amplio, una aportación adicional a esta línea de pensamiento. De acuerdo con ella, en el asma la coexistencia de estímulos inflamatorios adicionales, de localización pulmonar o extrapulmonar, agravan la evolución del proceso respiratorio. Los efectos de esos estímulos pueden ser aditivos o actuar de manera sinérgica con la propia inflamación asmática. Más allá de su interés práctico, la hipótesis viene a recordarnos que el organismo es un constructo conformado a partir de conjuntos interconectados, y que el asma incluye en su patogenia elementos de naturaleza diversa entrelazados. Si esto es así, el planteamiento futuro tendría que comenzar a centrarse en la búsqueda de los *hubs* de esa red llamada asma integrando la información aportada por la genómica, la proteómica y la metabolómica.

Introduction

The model for modern science arises from the reductionist-mechanistic Newtonian tradition in which the object under study is divided into simpler parts in the hope that, with these building blocks, we can elucidate the working of the whole, accepting that the sum of the solutions to a problem is also a solution.[1,2] This

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approach to learning about nature has undoubtedly yielded some extremely satisfactory results. However, the reductionist model does not always work well when the object under study: *a)* is not in thermodynamic equilibrium when it interacts with the environment; *b)* operates subject to nonlinear dynamics (effects are rarely directly proportional to the cause); and *c)* the whole cannot be represented as the sum of the parts because of the emergence of new properties that cannot be explained by simply summing these individual parts.[1,2] Living beings are more than the sum of their constituent atoms, from which the property of life itself emerges, and the human brain is not just the sum of its neurons, but rather gives rise to intelligence and consciousness. Nonlinear science or the science of complexity was born in the last century as a means of getting to grips with this holistic paradigm. Chaos theory, fractal geometry, cellular automatons, emerging computing, and network analysis, among others, can all be considered part of this nonlinear science.[2]

We believe that the application of some of these underlying principles of nonlinear science may improve our understanding of a complex disease such as asthma, in which many issues are still outstanding.

Current Barriers in the Management of Asthma

Although our knowledge of the pathogenesis of this disease has advanced considerably in recent decades and there have been substantial improvements in treatment, a cure remains elusive, and achieving acceptable control of the disease is not always easy in many patients. Asthma that is refractory to treatment or difficult to manage is a good example of this limitation.[3] In any disease, a number of reasons may be invoked to explain therapeutic failure (side effects of medication and pharmacogenetic or pharmacodynamic limitations of the drugs used, multiple pathogenic pathways, wrong therapeutic target, etc).[4] In the case of asthma, certain specific factors have been identified that are associated with poor outcomes: polymorphisms; sustained exposure to allergens, occupational agents, or environmental pollutants; rhinosinusopathy; lack of therapeutic compliance; psychosocial factors; lack of adherence to guidelines; inadequate perception of symptoms, etc (Table 1).[3,5-11] Even so, the truth is that the current approach to asthma still leaves many questions unaddressed. For example, Bjermer[12] recently considered the need to change treatment strategy because, as in the case of chronic obstructive pulmonary disease (COPD), asthma could be considered a systemic inflammatory disease. This is the only way to explain the associations detected between asthma and rhinitis, atopic dermatitis, inflammatory bowel disease, sleep disorders, and cardiovascular disease.[12] The HUNT and Young-HUNT studies, conducted in Norway, would seem to support this alternative pathogenesis by identifying the extent to which allergy is related to clinical manifestations that, on the face of it, are not strongly linked to the atopic phenomenon.[13,14] Extending this general approach, Pavord et al[15] have also put forward a further hypothesis, the so-called "multiple inflammatory hits" theory.

Table 1
Determinants of Refractory Asthma

Polymorphisms
β_2-adrenergic receptor
CRHR1
Interleukin-4
Environmental Factors
Allergen exposure
Exposure to occupational agents
Exposure to chemicals/contaminants
Comorbidities and Cofactors
Smoking habit
Rhinosinusopathy
Use of nonsteroidal antiinflammatory agents, β-blockers, angiotensin-converting enzyme inhibitors
Obstructive sleep apnea syndrome
Menstruation, pregnancy
Treatment nonadherence
Psychiatric diseases
Psychosocial circumstances
Alterations in perception of dyspnea
Multiple inflammatory hits

Abbreviation: CRHR1, corticotropin-releasing hormone receptor 1.

Multiple Inflammatory Hits and Asthma: Conceptual Framework

Theoretically, in asthma (as in COPD), the presence of additional inflammatory stimuli, located in the region of the lungs or at other sites in the organism, exacerbates and/or hinders improved outcomes of respiratory disease.[15] The effects of these stimuli may be additive or they may act synergistically with the inflammation associated with asthma itself. In the first instance, the final result will depend on the variations in the response of the host to those stimuli, on the site where the induced inflammatory response predominates (large or small airways), and on the type of cells implicated (neutrophils or eosinophils).[15] If this hypothesis were correct, then it should be theoretically possible to identify and modulate those additional inflammatory stimuli and slow the progression of the disease, which would otherwise advance to forms resistant to standard treatment.[15]

From our standpoint, the approaches of Bjermer[12] and Pavord et al[15] are an intelligent attempt to deal with a difficult question (the nature of asthma) whose interpretation, so far, has been based essentially on direct deterministic relationships (stimulus-inflammation-bronchial hyperresponsiveness-obstruction-symptoms) while neglecting the nonlinearity of certain effects. Why does hyperresponsiveness in the airway persist for months after a single exposure to allergens?[16] Why do patients with occupational asthma report persistent symptoms once they are no longer in contact with the environmental agent?[17] Why, at times, is the strength of the trigger only weakly correlated with the severity of the attack?[18] These and other similar questions have prompted some to think that the respiratory system, during the course of the disease and perhaps also in its normal healthy state, is comprised of multiple interacting parts and that such a system adopts a stochastic behavior with dynamic properties similar to those of other complex systems.[19-21] If this supposition is valid, and before going further with the theory of multiple inflammatory hits, it seems necessary to give a quick overview of what complex systems are and how they behave.

Complex Systems and Scale-Free Networks

A complex system is, by definition, a set of connected elements that form a whole with substantive characteristics not present in the individual parts, such that the final result of the interconnectivity produces new (emergent) qualities that cannot be attributed to the parts taken in isolation.[22,33] The larger the number of parts that make up the whole, the greater the complexity. All systems are embedded in an environment that may affect how they work and their end performance. Systems that exchange little or no material, energy, or information with the outside are known as closed systems whereas those that do interact with their environment are known as partially open or open systems.[22, 24,25] Likewise, within the category of open systems, some are passively influenced by the environment (nonadaptive systems) while others may react and adapt to the environment (adaptive systems).[22,24,25] The systems can also be divided into dynamic and static ones according to whether they modify their internal state over time. A system that, despite being in

contact with a changing environment, maintains its internal state is known as homeostatic. Highly homeostatic systems track changes in the environment through self-adjustments; if they do not manage to do this by modifying their structure or function, they will—to a greater or lesser extent—be transformed or deteriorate, either temporarily or permanently.[22,24,25]

Study of complex systems has been traditionally conducted using graphical mathematical methods, where each element of a network is known as a node or vertex, and connections between them are known as links or connections[22] (Figure 1). Nodes are denoted by the symbols *v1, v2…vN*, where *N* is the total number of nodes. When a node *vi* is connected to another node *vj*, this connection is represented by an ordered pair (*vi*, *vj*). If for each pair (*vi*, *vj*) there is a pair (*vj*, *vi*), the network is known as "undirected"; otherwise the network is known as "directed."[22] Analysis of the structural and topological properties of the system provides us with information on how nodes are connected to each other. Of these properties, particularly noteworthy are the following: *a)* the connectivity distribution P(*k*) (probability that a node chosen at random has *k* links or neighbors); *b)* the clustering coefficient *C* (probability that 2 nodes directly connected to another node are also linked to each other); *c)* the minimum length L_{ij} between 2 nodes v_i and v_j (minimum number of "jumps" needed to go from 1 node v_i of the network to another v_j); and *d)* average network length *L*, that is the average of the minimum lengths L_{ij} between all possible pairs of nodes (v_i v_j) of the network.[22,24] The first of these—the connectivity distribution P(*k*)—is perhaps the one that best characterizes the architecture of a given network.[22,24] Thus, there are basically 2 main types of complex networks: those with a Poisson topology and those with a scale-free topology.[22,24,26] The former, described by the Hungarian mathematicians Paul Erdös and Alfréd Rényi, are characterized by their homogeneous distribution of links among the nodes. Although some may have more connections than others, on average, they all have the same connectivity.[22,24,26] In contrast, the defining characteristic of scale-free networks is their high heterogeneity, with some nodes with few connections, some with an average number of connections, and some—known as hubs, that is, focal points—with many connections. In other words, in scale-free networks, the mean connectivity of the nodes is not representative of the actual connectivity of the network (Figure 2).[22,24,26]

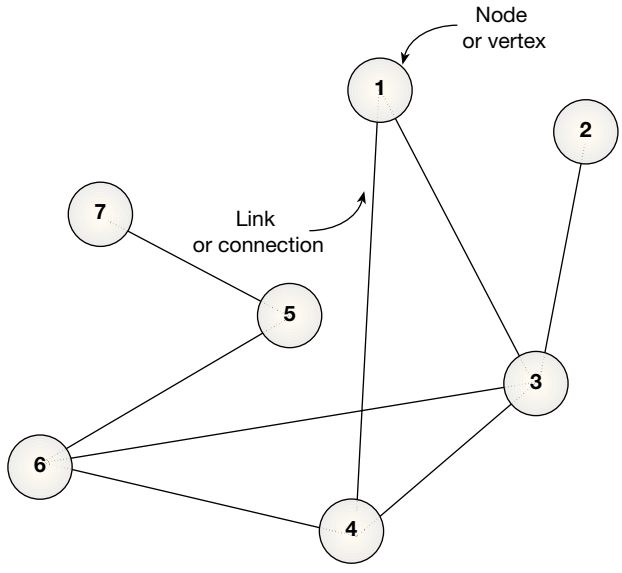

Figure 1. Schematic representation of a network with 7 nodes and 8 links. The set of nodes is *P* = {1, 2, 3, 4, 5, 6, 7}, and the set of links is *E* = {{1,3}, {1,4}, {2,3}, {3,4}, {3,6}, {4,6}, {6,5}, {5,7}}.

In addition, scale-free networks follow a power law distribution.[22,26] A relationship between 2 quantitative variables that obeys the power law indicates that the frequency of what is measured is a constant negative exponential function of the magnitude that is being measured. In other words, the number of events of a given magnitude N(*s*) varies according to the function $s^{-\gamma}$, where *s* is the magnitude of the event and γ the exponential constant. The relationship $N(s)=s^{-\gamma}$ is known as the power law because the number of events is a power of the magnitude of the event. The negative exponent implies that there will be a relatively large number of small events and a relatively small number of large events. The statistical distributions of the power law do not follow a normal (Gaussian) distribution as they lack a "central" value around which individual measurements are spread. A convenient way of investigating whether a power law applies is to plot the logarithm of the number of events [log *N(s)*] against the logarithm of the magnitude of events (log *s*) to see whether a straight line results. If this is the case, the gradient of the line will be equal to the exponent γ of the power law, that is: $\log N(s)=-\gamma \log s$ (Figure 3).[27]

One noteworthy feature arising from the special structure described above is that the connections are robust in the face of random suppression of nodes.[22,24] In this type of network, it is easier to eliminate a node with few connections than one with many connections, although if a hub is suppressed, the system may change, leading to fragmentation.[22,24] At the same time, the existence of these hubs means that information can arrive more quickly and easily (with fewer "jumps"), provided we select the most interconnected route. This circumstance (known as the small world phenomenon) indicates that the mean distance between any pair of nodes that are not directly connected is small.[22-24]

Leaving aside aspects of structure and design, in all likelihood the most relevant detail that experts in network theory have highlighted in comparative studies is that a large number of known complex systems adopt a scale-free topology. Examples include gene regulation networks, protein networks, metabolic networks, neuronal networks, communication and computing networks (Internet, telephone networks, etc), social networks (friendships, sexual contacts, scientific collaborations and authors of publications, disease propagation, etc), ecological networks (trophic interactions in an ecosystem), etc (Table 2).[22]

The fact that such different networks essentially share the same formal architecture has led some to hypothesize that they are governed by a fundamental law, at present unknown, and that such a design confers an evolutionary advantage, per se.[28] What is clear is that the adoption of scale-free networks by biological systems has beneficial consequences (facilitating chemical diversity at minimum energy cost, reducing the time of transition between metabolic states, reducing the consequences of biochemical or genetic errors, among others).[29]

What we have discussed so far might be considered to be a purely academic oddity, though nothing could be further from the truth. By applying the principles of nonlinear science, multivariate statistical procedures and computational models have managed to produce specific detailed maps of transcriptional regulation,[30] discover human diseases with surprising interconnections, for which the so-called diseasome is already being constructed,[29,31,32] identify new therapeutic targets that influence the propensity to and lethality of prostate adenocarcinoma,[33] design strategies to control epidemics,[34] and study the spread of obesity in certain population groups,[35] to give just some examples.

Thus, network and complex systems analysis recognizes links, helps illustrate the structure of the whole or subwholes and, at the same time, delves deeper into the nature of the relationships, clarifies the rules that govern those relationships, and erects new

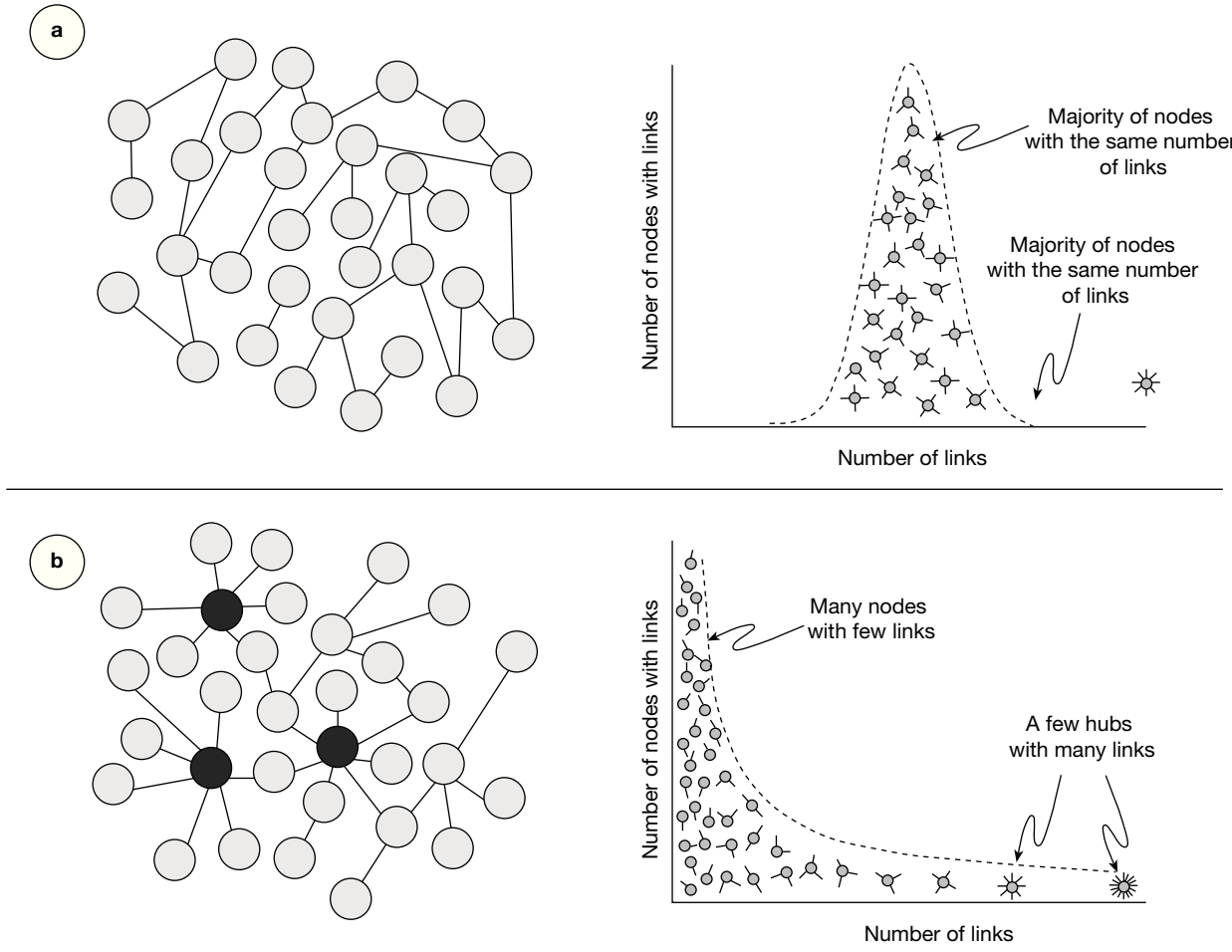

Figure 2. Examples of networks with Poisson topology *(a)* and scale-free topology *(b)*. In each case, the relationship between the number of nodes with links and the number of links (x axis) is shown.

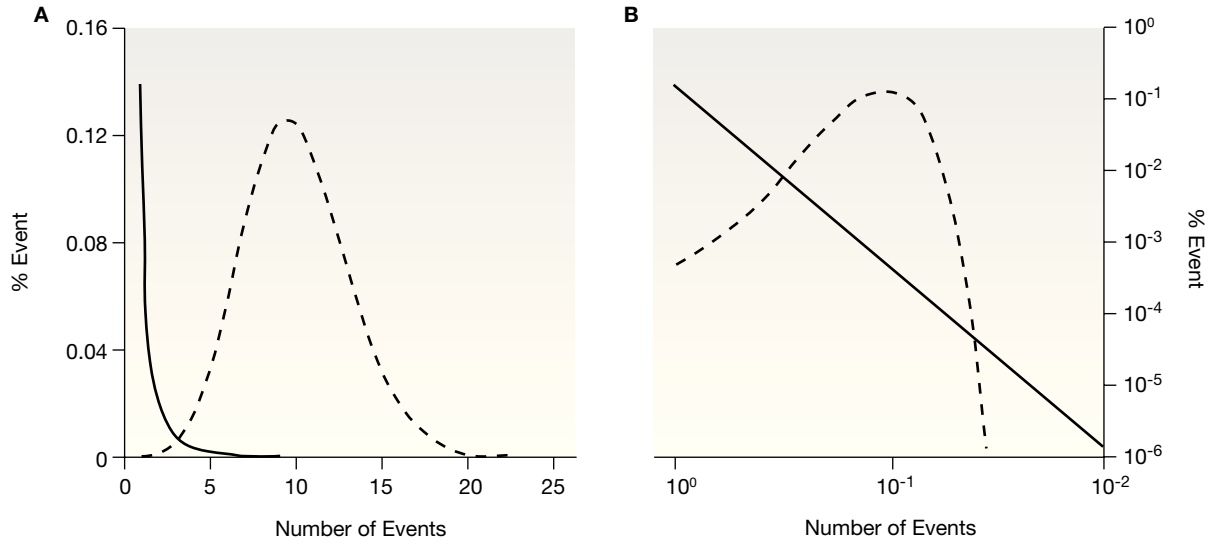

Figure 3. Comparison of a generic Poisson-type distribution (broken line) and another that fits the power law (solid line) using linear scales (*A*) and linear or logarithmic scales (*B*).

Table 2
Examples of Scale-Free Networks

Network	Nodes	Link
Cell metabolism	Molecules	Participation in the same biochemical reaction
Hollywood	Actors	Appearance in the same film
Internet	Routers	Optical and other physical connections
Protein-regulation network	Proteins that regulate cell activity	Protein-protein interactions
Collaboration in research	Scientists	Coauthorship of articles
Sexual relations	People	Sexual contact
World wide web	Web pages	URL addresses

investigational frameworks that can help provide all-embracing solutions as opposed to multiple deterministic problems.[36]

With regard to asthma, the current medical literature is still limited and focussed on describing the interactions between candidate proteins and genes implicated in its pathogenesis,[37,38] or on models predicting the onset of attacks starting from the premise that the airway has a fractal geometry.[39] In our opinion, the theory of multiple inflammatory hits, judged in its broadest sense, represents a contribution to this field.

Multiple Inflammatory Hits and Asthma: Development and Pathogenic Mechanisms

For Pavord et al[15]—leaving aside examples such as smoking[40] and the role of chronic or latent infections of the airways by viruses,[41,42] *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*[43]—the associations that would support their hypothesis would come from chronic inflammatory processes that affect organs embryologically related to the lungs. Examples of such processes include inflammatory bowel disease, chronic hepatitis C viral infection, autoimmune thyroid disease, and gastritis induced by *Helicobacter pylori*.[15] Nevertheless, perhaps the situation that best reflects the idea of multiple inflammatory hits is the association of asthma and hepatitis C. The hepatitis C virus is an RNA virus that belongs to the *Flaviviridae* family and that is well equipped for eluding the host's immune system. It causes persistent infection after most cases of acute infection. The persistence of infection is responsible for the direct or indirect actions of the virus on liver tissue, causing chronic inflammation that will progress to cirrhosis and hepatocellular carcinoma. Chronic infection is associated with many extrahepatic manifestations, including pulmonary ones.[44] Several studies conducted in Japan have managed to show that, in patients with asthma who are infected by the hepatitis C virus, the deterioration in lung function is accelerated and response to β_2-adrenergic agonists and inhaled corticosteroids is reduced while response to anticholinergics such as oxitropium is maintained.[45-47] The effects on lung function are also apparent in patients with COPD.[48] However, when patients with asthma and viral infection are treated with interferon and the viral load is reduced, the behavior of sympathomimetics and steroids tends to be similar to that found in patients who are not carriers, and the decline in peak expiratory flow in 1 second is reduced (Figure 4).[45,46] For the authors of those studies, what we have just described could be related to a virus-induced increase in $CD8^+$ T cell populations present in the respiratory system of asthma patients.[49] This would support the findings of other groups.[50,51]

Whatever the truth of the matter, according to Pavord et al,[15] their theory could be explained by considering that many of the inflammatory stimuli mentioned above have been associated with setting in motion of natural immune response, upregulation of the homing pathways, and activation of inflammatory cells (neutrophils and monocytes/macrophages). This would have repercussions in preexisting acute and chronic immune responses in the region of the lungs, leading to amplification and propagation.[15] We should bear in mind that natural and acquired immunity are engaged in a continuous 2-way communication, with so many connections that Sabroe et al[52] have proposed the idea of "contiguous immunity" in order to underline the phenomena of cooperation between the 2 types of immunity. Likewise, we should remember that in asthma (and in COPD, pulmonary fibrosis, and pneumonia), a process of recruitment and differentiation of bone-marrow-derived hematopoietic and mesenchymal progenitor cells occurs. These cells have the potential to differentiate into different cell types (antigen-presenting cells, granulocyte progenitors, endothelial cells, fibroblasts, myocytes, etc) able to "perceive" damaged tissue, migrate to the required site, and contribute to repair and remodeling after lung injury (Figure 5).[53] It is worth considering whether the opposite phenomenon might also occur in the face of extrapulmonary inflammation. Thus, induced progenitor cells may reach not only the region where they were produced, but also the airway, which, in the present supposition, is already undergoing its own inflammatory processes (of "asthmatic" nature in this case).

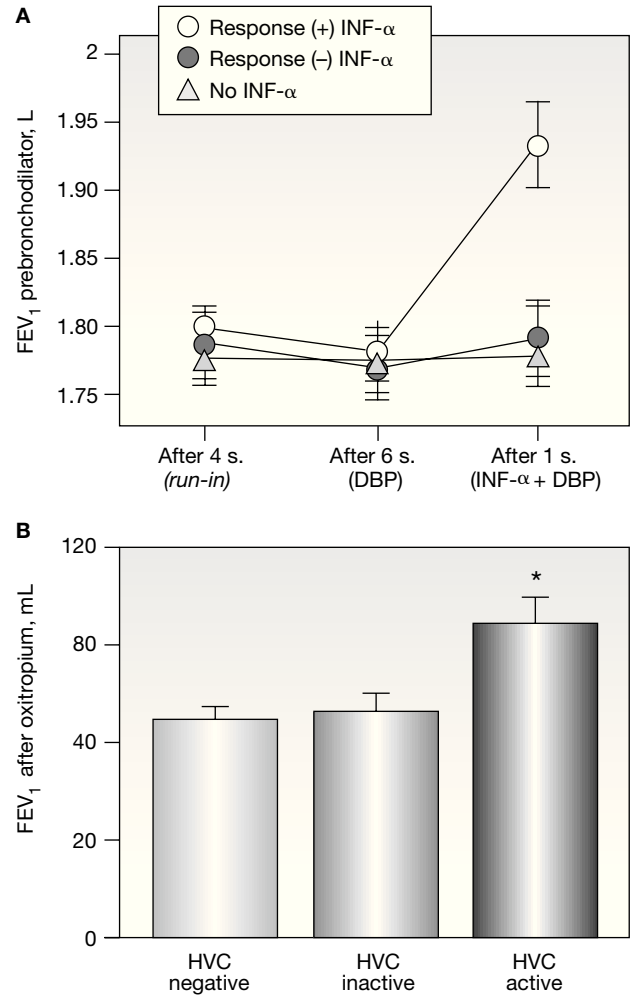

Figure 4. Infection by the hepatitis C virus (HCV) and asthma: effects on response to steroids and oxitropium. *A)* Change in forced expiratory volume in 1 second (FEV_1) after administration of bronchodilator to 48 patients with asthma and HCV infection treated with beclomethasone (BDB), of whom 30 also received interferon (IFN); only in 11 did treatment with IFN significantly reduce the viral load. After 1 year, FEV_1 in this latter group was clearly improved. *B)* Change in FEV_1 after administration of oxitropium to stable asthma patients without HCV infection and to asthma patients with active or inactive hepatitis due to HCV. Based on Kanazawa et al[45,47].

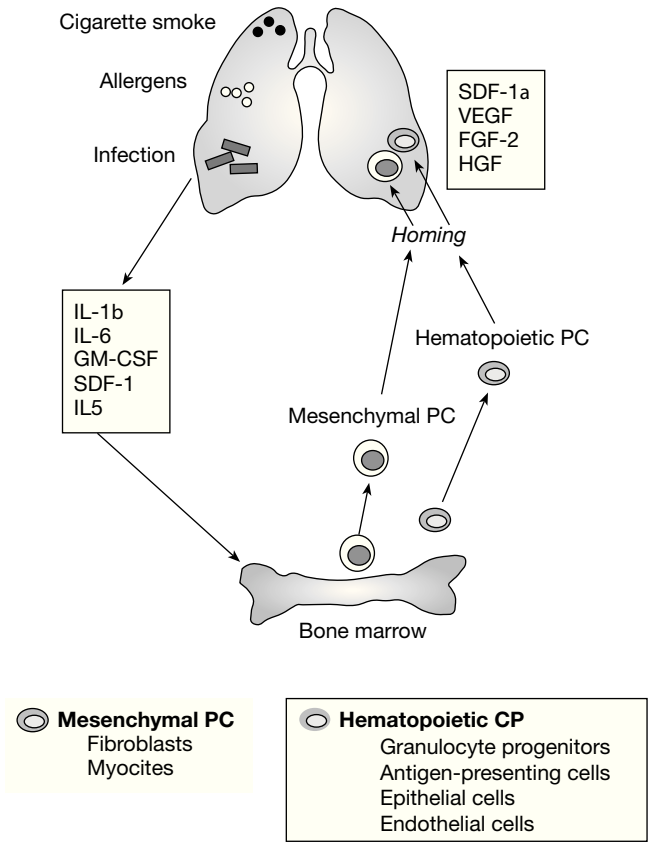

Figure 5. Diagram summarizing how lung inflammation induced by different stimuli generates mediators that stimulate production in bone marrow of hematopoietic and mesenchymal progenitor cells (PC) implicated in inflammatory response. Abbreviations: FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; HGF, hepatocyte growth factor; IL, interleukin; SDF, stromal-derived factor; VEGF, vascular endothelial growth factor. Based on Denburg and Van Eeden[5].

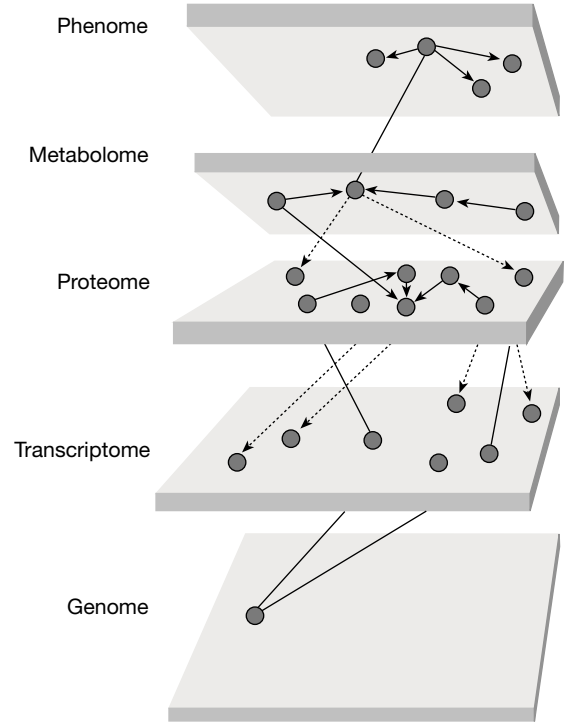

Figure 6. Integration and interrelations between data on gene expression (genome, transcriptome, proteome), metabolome (set of given metabolites), and phenome (set of physiological or pathological parameters of interest). Systems biology seeks to identify the interaction and relationships of all these data situated in different planes to provide an integrated vision of the problem under study. Modified from Lusis[56].

Final Points

Beyond the undoubted practical value (making sure the physician is aware of the need to rule out certain comorbidities in asthma), the greatest virtue of the hypothesis of multiple inflammatory hits lies in viewing the lung not just as an isolated organ and considering the organism as a construct of interconnected parts, that is, considering the pathogenesis of asthma as a complex entity which also includes elements of a diverse nature that apparently bear little relation to lung disease itself. This affirmation may appear obvious at first sight, and so it would be if we did not go deeper into the concept of complex systems whose structures adopt topologies of scale-free networks. To make this qualitative jump, we should think about where the hubs in this network called asthma actually are, assuming: *a)* that a component that acts as a hub in one process may play a different role in another, and *b)* that the importance of hubs may vary during the course of the disease and in acute and chronic situations. This strategy, still in its infancy, has started to be explored in COPD by Sabroe et al[4,54] in the hope that it will help in the identification and isolation of definitive therapeutic targets.

Certainly, in the coming years, we will see far-reaching changes in the way we study diseases. The biggest challenge will be to pool the wealth of information generated by genomics, proteomics, metabolomics, etc, along with the science of complex systems and systems biology,[55] into a framework that will make further study possible (Figure 6).[56] To paraphrase Solé,[57] complexity has more to do with the nature of the interactions than with the nature of the objects that interact, although these objects do impose certain limitations on what might occur at the next level. To understand complexity requires replacing the analytical approach with a way of looking at reality that includes the addition of an essential element: the map of connections between elements. We need this map to flesh out the integral interpretation of what we observe.

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