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LITERATURE Watch

Implications for transplantation

System Network: Tackling the Complexity of the Immune System

CITATION **Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet 2011; 12: 56-68.**

CITATION **Germain RN, Meier-Schellersheim M, Nita-Lazar A, Fraser ID. Systems biology in immunology: a computational modeling perspective. Annu Rev Immunol 2011; 29: 527-585.**

CITATION **Lee MJ, Ye AS, Gardino AK, Heijink AM, Sorger PK, MacBeath G, et al. Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks. Cell 2012; 149: 780-794.**

SUMMARY AND ANALYSIS

The reductionist approach in science has permitted the identification of innumerable genes, molecules and cells. These isolated discoveries have generated a very large dataset that is difficult to understand in totality. Focusing on single molecules or cells is like listening separately to notes of an individual instrument in a symphony, which fails to capture the ensemble effect achieved by the combination of instruments playing together. Newer sets of technological tools have further complicated the picture, so that microarrays and high-throughput screens generate a massive output of data. One of the greatest challenges of modern science is integrating all this knowledge so that it can be used to improve the understanding of disease processes and enable the development of novel biomarkers or drug targets. Building a network from the molecular and cellular components is the goal of the novel growing field of systems biology, whose concepts and potential applications to human disease have recently been reviewed by Barabasi et al.

Briefly, a biological network is composed of nodes (e.g. each individual molecule) and links, which represent the interactions between nodes of a network. Although one might assume that each node has approximately the same number of links (Figure 1A), biological networks are actually scale-free (Figure 1B). This means that there are a few nodes that are highly connected, termed hubs, which hold the whole network together. This facilitates transfer of molecular information across the system, accommodates perturbations with minimal adverse effects and promotes biological diversity. Networks have a high degree of clustering, in which molecules that are involved in similar functions have an increased tendency to interact with each other. In immunology, this means that the regulatory immune network forms a module, and disturbance of hubs of this network (e.g. CTLA4, Foxp3) leads to a significant dysregulation along with overlapping physiological consequences, while disturbance of more peripheral nodes (fewer links) leads to less prominent effects.

Systems biology uses bioinformatics to generate computer models. Building a biological network starts by inputting profiles of cellular transcripts that occur after manipulation of a particular molecule. There are currently many public databases covering genetic, protein and RNA networks that can be used as a starting point. The prediction of the computer model is then tested experimentally by manipulation of target components of the network and measurement of output information. The model is then updated based on the validation data, refining the performance of the model. This approach may overcome the failure to develop novel drug candidates relying solely on advances in conventional scientific experimentation. In addition, models will predict the consequences of multiple drug targeting as with immunosuppressive protocols used in our transplant recipients. This approach has been applied with success in oncology through the use of network signaling models to predict efficacy of drug combinations, ultimately optimizing anticancer therapy, as seen in work by Lee et al. Lastly, systems biology could integrate different scales of interactions, such as at the genetic, protein and cellular levels, to explain common phenotypes originating from diverse abnormalities.

Is systems biology going to substitute traditional experimental designs used to perform science today? Not really, but it will definitely help interpret experimental data that frequently do not take into account the complex, nonlinear structure of networks, such as the immune system, with its many parallel, overlapping and compensatory pathways. Computational models will always need to be validated with traditional scientific approaches. Germain et al. have reported specific data-gathering techniques and modeling tools that can be employed to answer relevant immunological questions.

We are currently driving on roads with a fragmented knowledge of the road map. Detailing the immune network will permit us to draw this map and help us embrace the complexity, understand the big picture and better translate discoveries into tangible clinical benefits. AJT

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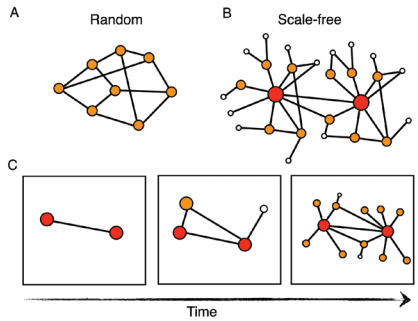

Figure 1: Structure of networks. A biological network is not randomly wired (similar number of links between nodes) (**A**), but follows a scale-free property, with central nodes that are highly connected (hubs) and less connected peripheral ones (**B**). When a network is being formed (**C**), the rich-gets-richer process is observed, so that highly connected nodes acquire more links than those that are less connected, leading to the natural emergence of a few highly connected hubs. Most biological hubs are essential to network homeostasis so that alterations lead to disruption of the network and lethality to the organism. This network property is not exclusive to biology, but can be found in other networks such as social (Facebook) or scientific collaborations. Panel C illustrates how a research collaboration network may develop over time with the emergence of a clear hub (established researcher) surrounded by nodes (collaborators), consistent with a scale-free property.