Translational Potential of Systems-Based Models of Inflammation

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Abstract

A critical goal of translational research is to convert basic science to clinically relevant actions related to disease prevention, diagnosis, and eventually enable physicians to identify and evaluate treatment strategies. Integrated initiatives are identified as valuable in uncovering the mechanism underpinning the progression of human diseases. Tremendous opportunities have emerged in the context of systems biology that aims at the deconvolution of complex phenomena to their constituent elements and the quantification of the dynamic interactions between these components through the development of appropriate computational and mathematical models. In this review, we discuss the potential role systems-based translation research can have in the quest to better understand and modulate the inflammatory response.

Introduction

Bacterial infection, trauma, surgery, and biological stressors in general, induce an acute inflammatory response characterized by a cascade of events during which multiple cell types are deployed to locate pathogens, recruit cells and eventually eliminate the offenders, thus restoring homeostasis. Under normal circumstances, this inflammatory response is self-limited, and once the pathogens are cleared, reparative processes begin and the response then abates.[1] Oftentimes pro-inflammatory responses prevail or anti-inflammatory processes fail, and an amplified runaway inflammation turns what is normally a beneficial reparative process into a detrimental physiological state. One component of the systemic inflammatory response is a hypermetabolic state which is characterized by significant alterations in the utilization of amino acids, glucose, and fatty acids, leading to increased resting energy expenditure, a negative nitrogen balance, hyperglycemia, and hyperlactatemia. This results in net muscle protein catabolism with extensive amino acid deamination and oxidation, as well as "futile cycling" of substrates such as glucose and fatty acids.[3]

Depending on the severity of the injury and success of treatment, hypermetabolism and other changes associated with the systemic inflammatory response can progress to multiple organ dysfunction syndrome and sepsis, characterized by significant morbidity and mortality rates.[4,5] Sepsis, the combination of infection and a systemic inflammatory response,[6] is generally accepted to result from an amplified body-wide inflammatory response,[7] and this disease has a substantial impact on healthcare expenditures with an annual incidence exceeding 750,000 cases, an approximately 25% in-hospital mortality rate and an average cost of over $20,000/case.[8] Such a mortality rate is translated to about 215,000 deaths annually nationwide making it the 10th leading cause of death in United States.[9,10]

Despite the growing understanding of the cellular and molecular mechanisms of the systemic inflammatory response syndrome[11] and the success of pre-clinical studies, not many effective therapies exist and few drugs are known to reduce mortality in clinical trials.[12–21] Thus, the intricacies in translating basic research to clinical practice are recognized as a challenge impeding the successful transfer of information from the pre-clinical to the clinical stage.[22,23] This challenge is often linked to the growing gap between basic and clinical research,[24] and there is growing interest to bridge the two through translational research. This term was coined by the American Physiological Society in an attempt to address complex pathophysiologies and was defined as the "transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing or treating disease as well as the transfer of clinical insights into hypotheses that can be tested and validated in the research lab."[24,25] To promote a systematic integration across multiple disciplines to help bridge this gap in the context of inflammation following traumatic injury, the NIH recently funded the development of a large-scale collaborative glue grant research program known as *Inflammation and the Host Response to Injury*.[26] Participating institutions include hospitals involved in clinical research studies, academic medical centers that perform analytical studies, and informatics and statistics centers that develop databases and analyze the voluminous data generated by the program. Furthermore, the current definition of NIH's Road Map to Medical Research[†] clearly identifies and states the importance of a deeper and better understanding of inflammation because it is broadly implicated in many diseases and conditions. Integrated initiatives are identified as valuable in uncovering as-yet-unknown immune mechanisms and mediators of inflammation as well as genetic factors, environmental triggers, and the relationship of inflammation to disease.

Tremendous opportunities emerge in the context of systems biology which aims at the deconvolution of complex phenomena to their constituent elements and the quantification of the dynamic interactions between these components through the development of appropriate computational and mathematical models.[27,28] Systems-based approaches are assisted by the availability of massive amounts of data related to dynamic cellular and molecular-level responses providing the underlying molecular signatures that drive macroscopic phenotypic observations.[29,30] Such information has dramatically accelerated the development of *in silico* disease models.[31] Mathematical models integrating the interacting elements of the unified inflammatory response offer the opportunity to establish a causal inference relationship through the manipulation of the corresponding dynamic elements.[32] Systems-based translational research considers physiological conditions as dynamically evolving "systems" with clearly identified boundaries and rules defining their responses.[33,34] As a result, there is a growing research effort toward

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the development of systems-based, quantitative models of the inflammatory response driven by the premise that such models can potentially enable the translation of knowledge from bench to bedside.[35]

Quantitative Models of Inflammation

One of the earliest mathematical models of inflammation dates back to the early 1980s when Lauffenburger and co-workers[32] described the local tissue inflammatory response to bacterial invasion. In this model, the leukocytes are continuously distributed while their accumulation and efficiency in localization within the inflammatory lesion, coupled with their phagocytic activity, determine the resolution of infection. This model expresses the dynamic interaction between the invader and a homogeneous leukocyte population using a two-variable model that consists of bacterial and leukocyte densities. An extension of this model replaced the single cell-target with a density number associated with the target population.[36] In this model, the principal goal was to address the effect of factors such as chemotaxis, cell speed, and persistence on target elimination dynamics. Further attempts[37] explored the interaction of the immune system with a target population (bacteria, viruses). Such analyses explored nonlinear interaction rules between the immune and target cells that determined the outcome of the immune response. Alternative modeling approaches placed emphasis on simulating interactions at the cellular level in response to an infection.[38]

Among the simplest, yet very informative, inflammation models incorporating measured quantities is the one proposed by Kumar et al.[39] The model tracks three basic variables indicative of the onset, progress, and resolution of the inflammatory response, which include the pathogen, and pro- and late-inflammatory mediators. Later, it was suggested[40,41] that the outcome of a healthy inflammatory response is determined by a balanced regulation in the dynamics of pro- and anti-inflammation. In a further refinement of this model,[42] the dynamic evolution of effector cells (macrophages, neutrophils) is distinguished from the corresponding activation of effector cytokines, and there is emphasis on the importance of modeling crucial signaling pathways (e.g., complement activation). Extension of this research effort focused toward the development of more generalized inflammatory models accounting for a diverse array of initiating events.[43,44] Models that describe the dynamics of the immune system in response to other infectious agents have also been proposed,[45] characterizing the rates of various processes contributing to the progression of the disease and focusing on the control of infection by the innate and adaptive immune systems.[46]

Recently, innovative computational approaches were proposed to integrate community-wide *in silico* models using the framework of agent-based modeling.[47,48] Such collaborative frameworks synthesize partial information into a unifying model that explores the complexity of the inflammatory response[49,50] based on the underlying principle of establishing rules among the actors of the biological response (agents).[51] Agents represent entities, such as cells and cytokines, which interact through the activation of local rules on a spatial grid of various probabilities.[52] Such models shed useful insight on the interacting elements that comprise the hosts' heterogeneity.

These mathematical models of inflammation do not systematically identify the elements that constitute an inflammatory response. The key characteristic of these models is the *a priori* postulation of certain components that are consistent with prior biological knowledge. This raises a very interesting question: what constitutes a critical component of the inflammatory response? This question becomes particularly relevant because of the tremendous progress in our ability to measure changes at the cellular and molecular lever[53–55] that can now generate data at enormous rates. A critical question is how to determine, based on large amounts of experimental data, which components constitute critical state variables that capture the essence of the response, reminiscent of the minimal model introduced early by Kalman.[56] In this direction, Foteinou et al.[57] introduced a systems-level approach which, based on the analysis of temporal gene expression responses, systematically identifies a critical set of dynamic features that are considered to be the elementary inflammatory responses triggered by an endotoxin stimulus in peripheral blood leukocytes (PBLs). The elementary responses are incorporated into an indirect response model that propagates the external signal (endotoxin) through a web of intracellular interactions. Such a model combines essential activation steps related to the innate immune system (recognition of the pathogen-derived product by pattern recognition receptors) with the adaptive inflammatory responses thus offering a mechanistic insight of the dynamics that are triggered at the cellular level in PBLs in response to the endotoxin stimulus.

Discussion

A critical goal of translational research is to convert novel insights from basic science to clinically relevant actions related to disease prevention, diagnosis, and eventually enable physicians to identify and evaluate treatment strategies.[58,43,44,49,59–61] It is important to realize that *in silico* models will never replace either biological or clinical research. They could, however, rationalize the decision-making process by establishing the range of validity and predictability of intervention strategies. Mathematical models can provide a synthetic framework that not only can reproduce dynamic behaviors that are in compliance with the inflammatory process but also can be predictive in the setting of population dynamics. The aforementioned models give a mechanistic insight about the behavior of the entire system through the dynamic integration of a set of key elements and, therefore, offer the possibility of exploring the inflammatory effect of various modes of intervention suggesting beneficial treatment schedules related to drug dose, type of intervention and administration, and patient selection. These quantitative representations of inflammation are a mechanistic extension of disease progression models[62] used in clinical settings to evaluate the effect of a drug action based on the state of a biomarker that serves as the surrogate for the disease state. In models of inflammation, the state of the disease is not expressed solely based on monitoring the response of a variable, but rather the inflammatory trajectory is determined by the dynamic evolution of its elementary components and their dynamic interplay. Among the possible benefits of the translational potential of mathematical models, we identify two: (1) the possibility of formulating testable hypotheses regarding the control of the inflammatory response; (2) the possibility of rational design of clinical trials.

The modeling work discussed in Refs. 43, 44, and 61 illustrates how modeling provides significant insight in terms of hypothesis generation. These studies demonstrate how hypotheses can be formulated, for instance, that LPS may not mediate hemorrhagic shock-induced inflammation via the classic CD14-TLR4 pathway,

and have also been pivotal in supporting the hypothesis that shock states induced by a wide range of physiological challenges are the emergent result of a universal response despite differences in initiation and modulation.

The work discussed in Refs. 42 and 59 established an important observation characteristic of a significant number of translational attempts, viz, promising therapies in animal models were, in general, not successful in clinical trials. Using as their starting point the failure of neutralizing antibodies directed against the pro-inflammatory cytokine TNF, these previous studies suggest how models can potentially improve case selection in clinical trials to evaluate the therapeutic consequence of various immunomodulatory strategies. The sampling of the parameter space defining the model allows for the generation of a cohort of "virtual" patients whose differing values correspond to different patient physiological characteristics. The simulated pool of various patterns in the model elements[42,59] allows one to further classify "patients" based on their response to a given intervention strategy. These results shed insight on optimal patient selection that is expected to benefit from an immunomodulatory strategy. As a result, the *in silico* trials could elucidate the reasons for such a failure of TNF neutralization therapy and suggest the design of future trials focusing on patients that are likely to benefit by such treatment. Finally, this could lead to a reassessment of the original results of the randomized clinical trials.

Systems modeling approaches may also provide reliable means for identifying multiple drug targets and thereby making this approach a critical enabler for understanding the effect of pharmacological interventions that span various scales of biological complexity.[28] Along this direction, Kitano et al. discuss the potential of a systems level analysis to develop improved approaches toward balancing the progression of complex (systemic level) diseases.[63] Effectively, the authors place emphasis on simulating the effect of targeting multiple cell types and pathways rather than single molecules. Although validating experimentally such *in silico* "predictions" is a non-trivial task, it is widely accepted[32] that it is too difficult, at least at present, to unravel such threads experimentally. However, the development of systems-based models allows an understanding as to how the system responds to a multitude of external perturbations and thereby can facilitate the clinical decision-making process.

Conclusions

Almost 40 years ago, a pioneering symposium was held at Case Western University to assess past developments and future potential of systems approaches in biology. Eloquently, Mesarovic[64] presented two important roles systems theory could play in biology:

(i) to develop general systems models that can be used as the first step toward arriving at a more detailed representation of the biological system, and
(ii) to provide a basis for communication between different fields because the formal concepts of behavior are defined in a precise manner, and in defining minimal mathematical structures reflecting the minimal degree of special features of the real-life system from which the formal concepts have been abstracted.

The main focus of this review was related to (i) because the discussion focused on how quantitative models of inflammation can be used as minimal representations of biological reality to formulate and test hypotheses, reconcile observations, and guide future experimental design. The translational potential of these quantitative models is coupled with research attempts to improve real-time diagnostics with the aim to monitor the immunologic state of a patient.[65] Therefore, the design of diagnostic devices strengthens the usefulness of mathematical models of inflammation in that they can, potentially, predict the dynamics of this complex process at an individual level thus guiding therapeutic interventions.[66–70]

However, (ii) must not be overlooked. The success of systems-based research is that through the universal language of mathematics and the opportunity to formalize and quantify complex physiological phenomena, oftentimes with significant simplifications, the systems approach has managed to establish communication bridges between scientists from a variety of fields. The majority of the examples discussed in this review are the outgrowth of coordinated efforts of biologists, biochemists, clinicians, mathematicians, engineers, statisticians, and computer scientists. This could be one of the most significant successes of systems-based translational research.

There exist, however, noteworthy challenges facing systems modeling that need to be further explored. Modeling the signal flow within and between cells is a significant challenge in modern biology[71] as it would accelerate hypothesis generation and testing while taking multiple cellular interactions into account. Although modeling the dynamic progression of a disease process is becoming increasingly important in drug development, as it provides a mathematical structure by which predictions of drug efficacy and safety in humans can be evaluated,[72] developing such models would require the identification of biomarkers that can adequately represent the response of the system. For complex homeostatic mechanisms, this would imply a multitude of biomarkers characterizing the progression across a cascade of compartments. Finally, an important aspect of "translational" research is the development of mathematical models that would infer the relationship between monitored physiological variables and the determinants of cellular response.[73] Such an effort would enhance our understanding of the interactions between disease states and putative therapeutic interactions.

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