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Treatable traits and therapeutic targets: Goals for systems biology in infectious disease

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Abstract

Among the many medical applications of systems biology, we contend that infectious disease is one of the most important and tractable targets. We take the view that the complexity of the immune system is an inevitable consequence of its evolution, and this complexity has frustrated reductionist efforts to develop host-directed therapies for infection. However, since hosts vary widely in susceptibility and tolerance to infection, host-directed therapies are likely to be effective, by altering the biology of a susceptible host to induce a response more similar to a host who survives. Such therapies should exert minimal selection pressure on organisms, thus greatly decreasing the probability of pathogen resistance developing.

A systems medicine approach to infection has the potential to provide new solutions to old problems: to identify host traits that are potentially amenable to therapeutic intervention, and the host immune factors that could be targeted by host-directed therapies. Furthermore, undiscovered sub-groups with different responses to treatment are almost certain to exist among patients presenting with life-threatening infection, since this population is markedly clinically heterogeneous. A major driving force behind high-throughput clinical phenotyping studies is the aspiration that these subgroups, hitherto opaque to observation, may be observed in the data generated by new technologies. Subgroups of patients are unlikely to be static – serial clinical and biological phenotyping may reveal different trajectories through the pathophysiology of disease, in which different therapeutic approaches are required.

We suggest there are two major goals for systems biology in infection medicine: (1) to identify subgroups of patients that share treatable features; and, (2) to integrate high-throughput data from clinical and *in vitro* sources in order to predict tractable therapeutic targets with the potential to alter disease trajectories for individual patients.

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Introduction

Infection is the largest single cause of death in humans worldwide and many infectious agents provide relevant *in vitro* model systems that are both amenable to study with high-throughput techniques, and recapitulate key events in disease pathogenesis. In this review, we consider how systems biology approaches may be leveraged to address the major unmet needs in infection medicine in the 21st century, with the aim of improving outcomes for patients with infection. In clinical practice we are unable to therapeutically modulate the host immune response to infection, largely due to its inevitable complexity. Despite this, we contend that host-directed therapies have a high probability of success, since there is already considerable innate variation in host responses to infectious disease, ranging from extreme susceptibility, to complete resistance, and tolerance. Infectious diseases are survivable if you have the right genetics. The challenge is to make the same diseases survivable for patients who would otherwise succumb.

A systems medicine approach to infection has the potential to combine and integrate relevant signals from clinical, genomic, transcriptomic, proteomic and pathogen biology data to draw inferences about disease pathogenesis. Below we discuss examples of aspects of this approach applied to various infectious diseases, and suggest future goals for the application of systems biology to infection medicine.

Unmet needs for treating patients with infection

More than 70 years after the discovery of penicillin [1], this same drug is still a prominent weapon in our antibacterial armamentarium. More broadly, the concept underlying this therapeutic approach - attempting to eradicate the pathogen from a patient's body using antimicrobial drugs - remains the only effective treatment. Although spectacularly successful, the focus on the pathogen has two limitations.

Firstly, death frequently occurs in infectious disease despite effective antimicrobial therapy. Alongside the direct effects of microbial virulence factors, tissue

Box 1: Terminology

Term	Definition
Host-directed therapy	Therapeutic intervention to modulate an aspect of the host response to infection to alter the biology of a susceptible host to induce a response more similar to a host who survives.
Clinical syndrome	A collection of clinical symptoms and signs that tend to occur together. Depth of characterisation is limited by the range of observations available.
Disease	A clinical syndrome for which at least some of the underlying pathophysiological processes are thought to be known.
Subgroup	A smaller set within any population of patients, who are linked by some clinical feature or group of features.
Endotype	A subgroup within a population of patients who are distinguished by a shared disease process.
Treatable trait	The pathophysiological feature (or, in a looser sense, a biomarker or group of biomarkers for that feature) that determines whether a given therapy will improve a given patient's outcome. The same trait may be present in many different clinical syndromes or disease processes.

damage is also caused by the host immune response. Immune-mediated damage leading to respiratory, cardiovascular and renal failure (sepsis) continues even after eradication of the pathogen [2]. At present, no treatments exist to modify these deleterious aspects of the host immune response.

Secondly, antimicrobial resistance threatens to liberate pathogens from the range of our solitary weapon against them. Unless something changes, deaths from infection are predicted to soar, overtaking malignant disease even in developed countries by 2050 [3].

Therapies to modulate the host response to infection would have the theoretical advantage that, in addition to promoting survival in the presence of effective antimicrobials, a host-targeted therapy may exert a less powerful selection pressure on pathogens, and may be more difficult for a pathogen to evolve to overcome. In our view, the development of such therapies is well-suited to the application of systems approaches.

Inevitable complexity of the immune system

The human immune system is arguably the most complicated organ system in the body, encompassing numerous effectors, inter-related feedback loops and extensive redundancy. This complexity is unsurprising when considering that our immune system has evolved in the face of microbial virulence factors that directly interfere with regulatory and effector mechanisms. Examples of microbial interference with host immune mechanisms are numerous and diverse. For example, one of the first innate immune mechanisms encountered by many pathogens is phagocytosis, which serves to both prime the adaptive response and eliminate invading pathogens by intracellular killing. Pathogenic Yersinia species, a group of facultative intracellular pathogens, encode a type three secretion system to directly inject effector proteins into the host cell cytoplasm, modulating the cytoskeleton to prevent phagocytosis, and inducing apoptosis of immune cells and blocking the MAPK and NF-κB pathways to reduce cytokine production [4]. Another bacterium, *Pseudomonas aeruginosa*, secretes a protease that cleaves a host protein (corticosteroid-binding globulin) to release the corticosteroid hormone cortisol at the site of initial infection, incapacitating the local innate immune response [5]. Even the relatively tiny genome of the influenza A virus encodes a protein (NS1) which is non-essential for replication and seems to be dedicated to interfering with both the induction and action of the host antiviral interferon response by sequestering viral dsRNA, preventing activation of RIG-1 signalling and inhibiting protein kinase R and OAS/RNase L [6].

The adaptive response, mediated by T and B lymphocytes, is also a target. The human immunodeficiency virus encodes three proteins that each down-regulate cell surface MHC-1 expression by distinct mechanisms, preventing MHC-I signalling to activate the cytotoxic T-cell response to virus-infected cells [7]. To prevent B-cells mounting an antibody response to infection, the *Staphylococcus aureus* surface protein A binds to the Fc-γ portion of antibodies [8].

These examples cover a few of the mechanisms pathogens have evolved to extensively interfere with the host immune response. The animal innate immune system is thought to have evolved over 1000 million years, starting with amebae able to phagocytose external material for nutrition [9]. The adaptive immune system in mammals is thought to have arisen 500 million years ago in fish [10]. Since these initial events, the immune system in each host species has participated in a genetic arms race, evolving alongside relentless exposure to these microbial immune interference strategies from innumerable pathogens. Furthermore, the immune system must successfully distinguish self from non-self antigens, with deleterious consequences arising (i.e. autoimmune disease) when this fails. The requirement to overcome these microbial immune interference strategies whilst preserving the recognition of self-antigens has provided the necessary pressure to drive the human immune system to evolve into a hugely complex organ system. In the context of this inevitable complexity, it is no surprise that reductionist approaches to development of host-targeted therapies in infectious disease have largely