Targeting the host immune response to fight infection

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Science **344**, 807 (2014);
DOI: 10.1126/science.1255074

more important correction that is related to the potential divergences in quantum gravity. In the 10-dimensional gravity theory, the first quantum correction would be divergent. In string theory, this divergence is removed by the presence of strings, but a finite local and calculable counterterm remains. This term gives a correction to the black hole entropy, and it is this particular correction that was matched by the numerical computation.

These quantum corrections had been previously computed in the context of extremal and near-extremal black holes [see, e.g., (*6*)]. These are charged black holes with the minimal or near-minimal mass, respectively, for a given charge. They are stable and do not emit Hawking radiation. In some cases, the previous computations even matched further subleading corrections. Hanada *et al.* can now match the corrections in a more generic finite-temperature situation. This calculation numerically tests quantum gravity in a context where string theory is crucial for obtaining the answer. In the usual quantization of gravity as an effective field theory, the correction that was considered would be proportional to an uncalculable counterterm. However, string theory provides a precise value for this counterterm (*7*) and is the one that reproduces a numerical computation with the interacting quantum oscillators.

In the near future, similar methods could also match the term that comes from the entropy of the Hawking radiation itself and eventually could match results for other observables in the thermal ensemble that probe more detailed aspects of the 10-dimensional geometry. This numerical test is further evidence of the internal consistency of string theory (i.e., that it does indeed provide a self-consistent quantization of gravity) and provides further evidence that the gauge/gravity duality is correct. Of course, the 10-dimensional space under consideration here is not the same as the four-dimensional region of the multiverse where we live. However, one could expect that such holographic descriptions might also be possible for a region like ours. ■

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10.1126/science.1254597

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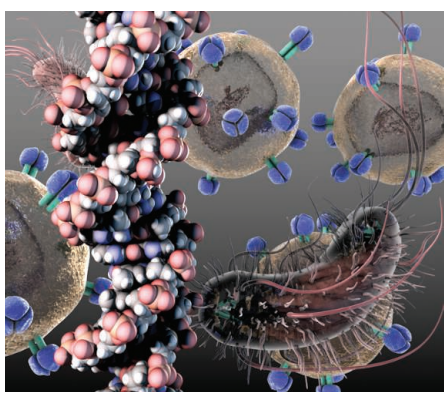
TRANSLATIONAL GENOMICS

Targeting the host immune response to fight infection

Strategies to modify immune responses to infection can be found in our genome

By **J. Kenneth Baillie**

Every year, infectious diseases kill millions of people worldwide. A close look at the modes of death from infection reveals something surprising: Often death is not attributable to a direct effect of the pathogen or of any toxin it produces; rather, it is the consequence of a systemic inflammatory response in the host (*1*). Our own immune system destroys us. This concept was observed long ago, but efforts to find effective therapies that alter the host response to infection to promote survival have largely failed.



Targeting the infectious agent is, at present, the only successful strategy, but the relentless emergence of antimicrobial resistance is an inevitable problem. Some pathogens, such as influenza virus, can evolve de novo resistance with terrifying speed (*2*). With hindsight, it is unsurprising that pharmacological interventions to alter the host response to infection have not been effective. Our immune system has evolved to fight a moving target. Whereas the job of the heart has changed little, and hemoglobin binds the same oxygen, and even the circuitry required to generate consciousness need not be different from that of our early ancestors, immunity must change rapidly, again and again, every time a new pathogen appears or an old pathogen mutates. By its very nature, the immune system is expected to be a mire of complexity, interdependence, and redundancy.

The core problem is finding the right element of an immune response to target with a drug. Even if we were to possess a full knowledge of every connection in an unimaginably vast network of interactions among cells, proteins, and nucleic acids that are required to generate an immune response, we would still be uncertain as to where to intervene to help patients survive infection. The good news is that evolution may have encoded within our genomes a shortcut to these targets.

"The core problem is finding the right element of an immune response to target with a drug ... When there is a way to confer a resistant state on a susceptible individual, the results have been impressive."

Susceptibility to infectious disease is one of the most strongly inherited of all common disease traits (*3*). Specific genetic variants confer susceptibility or resistance to infection. Knowledge of these variants presents us with a challenge: Here is the genetic code required for resistance; all we need to do is find a way to confer it upon susceptible individuals. Genetic susceptibility or resistance tells us the one thing we most want to know about any component of a complex system: What will be the effect of intervening here?

When there is a way to confer a resistant state on a susceptible individual, the results have been impressive. For example, a patient with HIV became resistant to the virus after a bone marrow transplant with cells from a donor whose cells were resistant to the virus (*4*). In this case, the patient

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Translational genomics. Surveying the genomic variations in patients who are susceptible or resistant to infections should narrow down to key components of a complex immune response, in effect giving us the answer to the critical question: What will be the effect of intervening here?

had also developed leukemia, which was treated by killing his bone marrow before reconstituting his immune system from hematopoietic stem cells bearing the donor's phenotype—HIV resistance. Such extreme measures are not always necessary. A mutation that predisposed patients to chronic infection with Epstein-Barr virus was recently discovered in a gene that encodes a magnesium transporter. Remarkably, treatment with magnesium seems to control the infection (*5*).

Recruiting the large numbers of patients required for genetic studies can be challenging, particularly in acute infections, which are by definition transient. But there are various methods to make the most of what we have. For example, studies of patients with extreme susceptibility to a disease, such as those who become critically ill, have greater statistical power to detect differences. Another consideration is to look in the right places in the genome. Disease variants are greatly enriched in protein-coding regions, and even more so in the regulatory sequences located outside of coding regions, where the activation state of a gene is controlled (*6*). Recent findings of the FANTOM (*7*) and ENCODE (*8*) projects have revealed where regulatory components lie in the human genome and in which conditions and cell types they are active. In some cases, inferences can be drawn from the pattern of gene expression across different cell types to better comprehend the roles of newly discovered genes. These patterns also provide new insights about the roles of the regulatory elements—more abundant than protein-coding genes by a factor of 10—that govern gene expression (*7*). These analyses suggest compelling candidate susceptibility genes.

Rather than studying the response of the entire host, a conceptually narrower approach is to study the host factors that restrict pathogen replication in cultured cells. The full complexity of the immune system is absent from these models, leaving two categories of host genes: innate intracellular defenses, such as the antiviral gene encoding interferon-induced transmembrane protein 3 (*IFITM3*) (*9*) or components of host cells that are required by the pathogen to survive and replicate. For example, viruses co-opt host proteins to perform essential functions in the viral life cycle. For specific pathogens, high-throughput studies that systematically silence large numbers of genes in vitro, one by one, can identify genes in both of these categories (*10*). This has been done with hepatitis C, for example, demonstrating that the host protein cyclophilin A is required for viral replication (*11*). This protein was already the target of a new therapy for hepatitis C, which is now in clinical trials.

These studies capitalize on a uniquely useful feature of intracellular infections—the ability of the pathogen to replicate in cultured cells. Replication has direct relevance to the clinical scenario at the bedside: If a patient's cells can be made less hospitable to the infectious agent, then it is at least plausible, if not likely, that an improvement in their clinical condition will follow.

If identifying a drug target is the goal, it is important to remember that it is easier to break a complex system than to improve it. The genetic causes of major immunodeficiency syndromes tend to be deficiencies in specific critical components of immunity (*12*). Replacing the function of these components, such as in patients lacking a key class of immune cells, is technically challenging and may not lead to improved resistance in individuals who already carry a functional copy of the gene. Patients born lacking the capacity to make adequate antibodies respond very well to antibody replacement (*13*), but (with a few exceptions) treatment with nonspecific antibodies is not effective in immune-competent patients with severe infections (*14*).

Mutations in less critical components of a system may flag better targets. One possibility is the IFITM3 gene, in which a variant associated with less IFITM3 protein production is more common in life-threatening influenza. In cell lines derived from people who possess the susceptible genetic variant, IFITM3 production is restored by treatment with interferon (*15*). Because it is generally easier to create drugs that inhibit proteins, gain-of-function mutations that cause disease are given priority. To efficiently find targets that meet these criteria will require integrating data from the sources such as those described above.

When a patient dies of an infection, we rarely pause to think that a weakness for that specific pathogen may have been present in that individual, right from the start, encoded in their genome. By interrogating these weaknesses, we are finding clues that may, in time, help us to save more people from the same fate. ■

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