Personalized Medicine for Sepsis

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Abstract: Sepsis is a complex syndrome triggered by infection and characterized by systemic deregulation of immune and inflammatory pathways. It is a major cause of death worldwide and results in the widespread use of antibiotics and substantial health care costs. In a vicious circle, sepsis treatment promotes the emergence of highly virulent and resistant pathogens and devastating nosocomial infections. Sepsis is a heterogeneous disease affecting many people worldwide. Because individual patients have different inflammatory responses and unique profiles of immune activation against pathogens, the most effective way to advance the treatment of sepsis is probably through a tailored approach. The advent of high-throughput technologies and the remarkable progress in the field of bioinformatics has allowed the subclassification of many pathological conditions. This has potential to provide better understanding of life-threatening infections in people. The study of host factors, however, needs to be integrated with studies on bacterial signaling in both symbiotic and pathogenic bacteria. Sepsis is certainly the sum of multiple host-microbial interactions and the metagenome should be extensively investigated. Personalized medicine is probably the only strategy able to deconstruct and reassemble our knowledge about sepsis, and its use should allow us to understand and manipulate sepsis as a wide, interconnected phenomenon with myriad variables and peculiarities. In this study, the recent advances in this area, the major challenges that remain, and the reasons why the septic patient should be approached as a superorganism are discussed.

Key Indexing Terms: Bioinformatics; Genetics; Genomics; Immunity; Pathogen; Personalized medicine; Sepsis. **[Am J Med Sci 2015;350 (5):409–413.]**

Sepsis is a heterogeneous disease affecting a wide spectrum of individuals ranging from healthy young trauma victims to aged patients with decompensated chronic comorbidities. Immune status, genetic predisposition, health history, pathogen type, and the site and extent of infection all vary in patients with sepsis.[1] Indeed, responses to sepsis vary between patients and within the same patient over time. The basic elements of treatment for sepsis have not changed in the past 50 years[2] and involve tailoring an appropriate drug therapy to the critically ill person, and infusing the drug at an optimal dose; however, getting the timing right is critical if the patient is to survive.

However, in the past few years, high-throughput technologies have advanced our understanding of sepsis at a molecular level. The most important is the emergence of solid, irrefutable data pointing out the nonexistence of counterregulatory antagonistic response syndrome. It has become clear that sepsis is not a biphasic disease, characterized by a massive inflammatory phase, followed by immune suppression. DNA microarray studies, on different populations and under various conditions, have shown that the immune-inflammatory pattern in sepsis follows an elliptic curve, with activation of innate pathways and concomitant repression of adaptive immunity occurring at the very beginning of sepsis and lasting until the patient dies or recovers.[3,4]

PATIENT SCREENING: TREATING AND MONITORING PATIENTS WITH SEPSIS

Genetic variation influences the risk of disease and its clinical evolution.[5] Such variation has been investigated intensively in the search for biomarkers that can direct treatment or lead to novel therapeutic avenues. Understanding genetic diversity is essential for advancing our comprehension of the molecular basis of complex diseases and how people respond to treatment as a population or as individuals.[6] Genomic-wide association studies (GWAS) have given us the ability to assay genetic variants that are common in a population and identify those that may be associated with a particular disease[7]; this has important implications for drug development. At present, 176 drugs approved by the U.S. Food and Drug Administration for the treatment of a wide range of diseases already contain pharmacogenomic information in their product descriptions.[8] In the field of sepsis, however, only a single GWAS has been published to date,[9] although many genetic polymorphisms have been individually investigated. To date, the single nucleotide polymorphisms implicated in sepsis pathophysiology are those of tumor necrosis factor, migration inhibitory factor, plasminogen activator-1, and toll-like receptors genes.

Rare variants and copy number variations in humans may also have important implications for the susceptibility to infectious diseases.[10] They are not, however, well-tagged common alleles at single nucleotide polymorphisms and are, therefore, not assayed well by current GWAS approaches.[11] For sepsis, studies investigating genome-wide rare variants or copy number variations have not been published yet. Gene copy number differences play a crucial role in the evolution of genome complexity and their rates in populations are much higher than point mutations,[12] although the vast majority of gene duplications have no functional effects and are removed by natural selection.

Treatment with a targeted therapy induces selective pressures that may promote unexpected behavior in bacterial pathogens. Thus, a tailored approach for sepsis should focus ideally on multiple targets to curtail the ability of bacteria to corrupt host defenses. Nanoparticles are an attractive tool for antibiotic delivery and manipulation of the local immune-inflammatory response.[13,14] These particles circumvent problematic drawbacks in conventional drugs, such as bacterial resistance and drug toxicity. Nitric oxide-releasing, chitosan-containing, and metal-containing nanoparticles use multiple mechanisms simultaneously to combat microbes.[15] Packaging multiple drugs within the same nanoparticle also makes the development of drug resistance unlikely[16] by targeting the site

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Submitted May 27, 2015; accepted in revised form July 17, 2015.

F.P.d.S. is supported by the National Council for Scientific and Technological Development (CNPq, Grant 470539/2013-15). The other author has no financial or other conflicts of interest to disclose.

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of infection so that higher doses can be administrated with fewer adverse effects.

Moreover, each patient has a different combination of mutations that predispose or protect them from sepsis and dictate the presentation and course of the disease. It is becoming evident that a single biomarker cannot successfully discriminate sepsis from noninfectious inflammatory conditions; hence, various combinations of biomarkers are being increasingly investigated.[17–20]

GENETIC VARIANTS AND THEIR CLINICAL IMPLICATIONS

Unfortunately, most genomic research studies have concentrated on populations of European ancestry and this has led to biased results.[21] Although common variants are found among most human populations, it has long been known that rarer genetic variants show widely differing patterns across different groups of humans.[5] It remains unclear whether such mutations accumulated through selective pressures under specific conditions during the last thousand years or have emerged more recently. It is also unclear how important they are in the generation of complex diseases. In any case, it is necessary to understand that human populations are not homogeneous, and that studies on genetic variation must address the enormous range of variation in our species. Human genetic variations have to be approached as a global phenomenon with regional peculiarities that do not support the definition of "race" in a taxonomic sense, because interindividual genetic variability is very large even among individuals from the same population. In fact, several studies suggest that ancestral African populations were genetically differentiated even before the expansion of modern humans from Africa approximately 70,000 years ago[22–25] (Figure 1).

There is a wide consensus among evolutionary biologists that race is a social and psychological concept. Racial classification of humans has no scientific value. It is true that there is a clear geographical structure in the genetic diversity present in the human genome, but only a minimal fraction of alleles and a small fraction of allele combinations are restricted to a single geographical region, and the within-population diversity is enormous.[26] Racial labels obscure important differences between patients, although it has proven utility for clinical stratification in numerous respects: screening for sickle cell anemia, cystic fibrosis, prostate cancer, Tay-Sachs disease, arterial hypertension, among others. Indeed, the Human Genome Project states that "People who have lived in the same geographic region for many generations may have some alleles in common, but no allele will be found in all members of one population and in no members of any other."[27]

LARGE-SCALE STRATEGIES FOR INVESTIGATING SEPTIC SHOCK

Large-scale genomic, transcriptomic, metabolomic, and proteomic reference libraries for drug and biomarker development should be produced to better understand the mechanisms involved in the complex scenario ie, sepsis. Interestingly, protein profiling in different tissues found that only approximately 3,000 of the 20,500 cataloged proteins are tissue specific, suggesting that a cell phenotype appears to be based more on the differential expression levels of proteins rather than on qualitative differences.[28]

Because the human genome is thought to be relatively stable throughout a person's life, it will gradually become more attractive to retain data from genome sequencing for future use. The cost-effectiveness of personalized exome and genome sequencing will improve with time, and genomic information will probably be integrated into medical health records.[29] Moreover, combining genomic sequencing with RNA sequencing and proteomic and metabolomic data will help us to interpret the clinical relevance of genome variations,[30,31] although this kind of integrative analysis is probably our biggest challenge at present.[32] In effect, the gene expression of sepsis is profoundly dynamic in human and animal studies and we agree that the idea of gene expression-tailored sepsis seems implausible at the near future, but its exploration in conjunction with other high-throughput techniques will certainly have unprecedented value.

DNA microarray data have permitted the subcharacterization of lymphomas and glioblastomas,[33] and the same approach can allow molecular classification of sepsis patient subsets. Indeed, a recent publication reported a DNA microarray method to subclassify children with septic shock based on genes that correspond to adaptive immunity and glucocorticoid receptor signaling.[34] Similar studies aimed at identifying critical aspects of sepsis subpopulations are in development with many researchers.

Investigating host factors, however, may lead to incomplete understanding of sepsis biology. Sepsis is certainly the sum of multiple host-microbial interactions, and the metagenome must be investigated extensively to search for mutations on both sides of this relationship that could affect the molecular profile, diagnosis, treatment, and prognosis of septic shock.

METAGENOME: THE SEPTIC PATIENT AS A SUPERORGANISM

Gut microbiota are a source of trophic, metabolic, and protective signals from which the host benefits.[35] The gut microbiome possibly contains 150 times more genes than human genomes[36] and displays high interpersonal variation,[37–39] making the tailored use of probiotics and prebiotics an attractive option to prevent and treat septic shock in humans.[40–42] Certainly,

FIGURE 1. Human migration map: expansion of modern humans from Africa approximately 70,000 years ago.